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American Heart Journal

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American Heart Journal

JULY 1972

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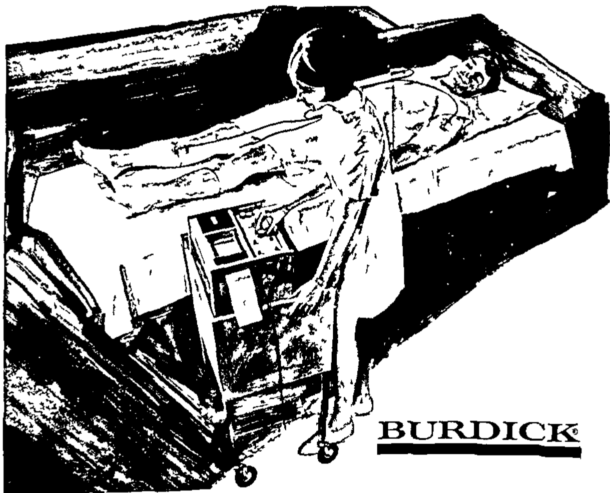
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in cardiac edema*

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augments the effects of other diuretics— combined with another diuretic Dyrenium can augment diuresis and natriuresis with lower doses of each agent [2]

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***Indications Edema associated with congestive heart failure cirrhosis and nephrotic syndrome steroid induced edema idiopathic edema edema due to secondary hyper aldosteronism and edema resistant to other diuretic therapy**

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Supplied 100 mg capsules in bottles of 100

1 Ross E J Aldosterone and Its Antagonists *Clin Pharmacol & Therap* 6 65 (Jan Feb) 1965
2 Earley L E Edema Formation and the Use of Diuretics *California Med* 114 56 (Mar) 1971

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American Heart Journal

July 1972 Volume 84 Number 1

Editorial

Hypertension in children

Sol Londe M D
David Goldring M D
St Louis Mo

The notion that hypertension of unknown etiology is uncommon in children has been commented upon in the pediatric literature for some time[1-5] However in 1966 Tackeuchi[6] after mass determinations of blood pressure in Japan reported that essential hypertension may start at an earlier age than was previously thought More recently in February 1971 Zinner and his co workers[7] concluded from their studies that a familial influence on blood pressure can be detected in childhood and they postulated that the factors probably responsible for essential hypertension are acquired in childhood The results of our recently published investigation[8] of 74 hypertensive children add further evidence that this is probably the case

At the beginning of our studies the definition of hypertension in childhood presented a problem The published values for normal children varied widely and reliable standards for office practice were unavailable It was therefore first necessary to establish normal values The mean values standard deviations and the 80 and 90 per cent ranges for each sex and year of age were calculated for systolic and diastolic pressures based on normal children examined in office practice The population sample consisted of 795 boys and 798 girls 3 to 15 years of age Appropriate size wrap around cuffs and the mercury sphygmomanometer were used and the pressures were obtained in a standard manner[9,10]

Our investigations on the hypertensive children were an outgrowth of the above studies and were conducted on 74 children 4 to 18 years of age who were asymptomatic and who either came for routine physical examinations to the private office of one of the authors (S L) or to his office in the Pediatrics Department of the St Louis Labor Health Institute The elevated pressures noted in these patients were incidental findings

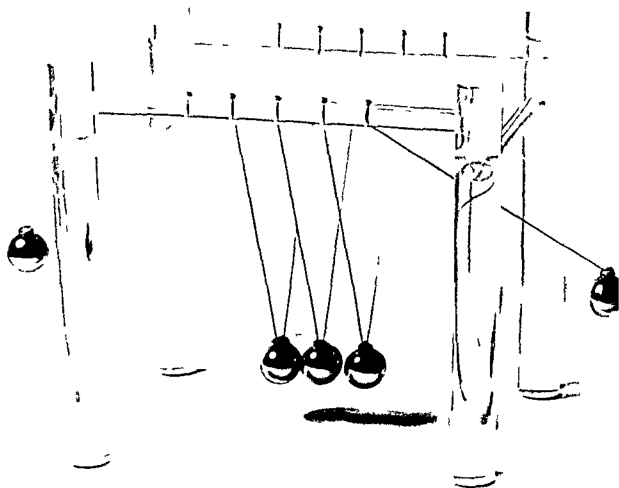
As suggested by Master and his co workers[11] in their studies of adult patients children whose systolic and/or diastolic blood pressures were repeatedly recorded above the ninetieth percentile and occasionally above the ninety fifth percentile for age and sex were classified as hypertensive All but 2 were under 15 years of age when their hypertension was first detected and they were followed for an average of 3½ years and in some cases for as long as 8 years The youngest age at which elevated pressure was observed was 3 years Only patients who were hypertensive for a year or longer were included in the study Laboratory studies for possi

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was 3 years Since we have documented elevated pressure as early as 3 years it is highly probable that hypertension may begin at an even earlier age The necessity for establishing reliable blood pressure standards from early infancy to 3 years of age is obvious There are now instruments available for the measurement of blood pressure in infancy [18] and it is hoped that pediatricians will make use of these new techniques Once reliable standards are established for this age group the question of how early hypertension appears may be answered

The much higher incidence of hypertension and cardiovascular disease among black adults than among white leads to the question of how early in life this difference appears Unfortunately there were not enough black children in the population studied by us to answer this question Rose [19] who compared black and white tenth grade children found no difference Whether this is true for younger children awaits further investigation

Our observations point to broader horizons for preventive pediatrics The importance of spotting an early tendency to hypertension needs no emphasis to the readers of this Journal However the importance of careful routine blood pressure determinations does need emphasizing to the practitioner treating children The implications from the public health standpoint are clear Furthermore just as the routine tuberculin test in the young sometimes leads to uncovering adult tuberculosis so may the finding of hypertension in children lead to the uncovering of hypertension in parents who may not have had blood pressure determination for a long time

The studies herein discussed also indicate the necessity of continuing extramural research on healthy populations as well as continuing research in medical centers which concern themselves mainly with sick people Only by continued observations of healthy infants and children will we be able to spot minor but significant deviations from the normal which may affect longevity

The educational campaign on the concept of risk factors in atherosclerosis and coronary artery disease which has been mounted by the American Heart Association has been aimed exclusively at the adult population It may well be that both these diseases as well as essential hypertension have their origin in infancy or childhood When more information becomes available and the pathogenesis of these diseases is better understood the risk factor campaign can be broadened to include the entire population Also it is of vital importance to attempt to develop through research the profile in infancy and childhood of the individual who is prone to develop atherosclerosis coronary artery disease or essential hypertension Hopefully this knowledge may eventually lead to effective prophylactic programs against these dreaded diseases

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ble causes of hypertension were performed on 33 individuals as outpatients Because of the paucity of abnormal findings in this group 41 patients were more extensively investigated as inpatients in the Clinical Research Unit of St Louis Children s Hospital

Possible causes for hypertension were found in only 5 patients who had abnormalities of the urinary tract The presence of obesity in 53 per cent of the children and a family history of parental hypertension in 44 per cent, however were significantly higher than in normotensive subjects The systolic and/or diastolic pressures were still elevated in 65 per cent of 46 patients who were followed for 3 to 8 years

The absence of an apparent cause for the hypertension in all but 5 of the patients, the high prevalence of obesity and of parental hypertension, and the persistence of elevated pressure in two thirds of the children followed for over 3 years, raises the question whether this type of juvenile hypertension is a prelude to essential hypertension in later life Additional studies by other investigators and continued study of our patients into adulthood may help clarify this perplexing question

Why has it been considered that hypertension in children is usually secondary? The reason may be the lack of a logical frame of reference for the practitioner taking blood pressures of children Because of this authors writing about juvenile hypertension have arbitrarily considered 135 to 140/85 to 90 mm Hg as the upper limit of normal However since these values are higher than the ninetieth percentile for children under the age of 10 years in our studies [9,10] younger children with moderately elevated blood pressures would have been excluded Furthermore whereas the patients in our study were asymptomatic children whose elevated pressures were incidental findings, the cases usually reported in the literature were hospitalized symptomatic and severely hypertensive children

As previously reported for both adults and children [12-15] the blood pressures of our patients fell after they were in the hospital Can it be that reliance on hospital blood pressure determinations alone may overlook children whose pressures may be moderately elevated in day to day life? Perhaps normal ranges for hospitalized children should also be established

Since intensive investigation revealed conditions possibly related to hypertension in only 7 per cent of our patients extensive and expensive hospital studies are not indicated in this type of child The following kind of outpatient study would seem reasonable inquiry for family history of hypertension complete physical examination, including lower extremity blood pressure determination blood and urine examination, creatinine clearance determination checks on serum potassium and urea nitrogen levels and a rapid sequence intravenous pyelogram

Recent evidence indicates that the treatment of adults with long standing essential hypertension reduces the risks of complications [16] Should treatment, therefore, be started in asymptomatic children with hypertension of unexplained origin? Probably not, because the pathogenesis of essential hypertension is as yet unknown, and there is no evidence at this time that these hypertensive children will develop fixed hypertension in later life Also the antihypertensive drugs have well known undesirable side effects and we question the wisdom of their use in growing children Finally there is no information available as to whether the institution of antihypertensive therapy in childhood hypertensives will prevent the progression of the disease It is known that obesity is a contributing factor and there is suggestive evidence that excessive sodium intake[17] may play a role There is therefore justification for recommending weight reduction in the hypertensive child and probably some reduction in his dietary salt intake These children should have annual physical examinations including funduscopic examinations and urinalysis From the standpoint of prophylaxis hypertensive parents should be apprised of the influence of heredity obesity and possibly of salt intake in essential hypertension It should be stressed that all advice be offered without creating needless anxiety

The youngest age at which we have been able to obtain reliable auscultatory blood pressure readings under office conditions

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Clinical communications

Blood pressures of !Kung bushmen in Northern Botswana

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About a dozen groups of people in the world do not show the rise of blood pressure with increasing age that is the average pattern in developed countries These groups have nearly all been found in remote parts of the world (Table I) But the observations that can be made on these communities far from medical school laboratories are not only of anthropological interest they may also contribute to our understanding of the nature and cause of essential hypertension The normotensive community we describe here has not been reported hitherto in the medical literature except for our preliminary communications[1,3]

Subjects and methods

We report here some of our investigations among bushmen of the !Kung tribe[4] in northwestern Ngamiland Botswana near the Aha Hills The 800 bushmen in this area have been kept isolated by a surrounding waterless zone 60 to 100 miles wide[5] They live as independent a life as any bushman group in existence today Many of them still live all the year round a hunter gatherers[6]

I DeVore and R B Lee of the Department of Social Relations Harvard University set up a camp next to the bushman camp near the Dobe waterhole in 1963 Since then except for the period 1965 6 the Harvard group has had one to three anthropologists living in the area usually for periods of about 2 years The resident scientists have learnt the !Kung language got to know the people and each has studied a different aspect of bushman life taking pains however to disturb it as little as possible Specialists have been brought to the camp from time to time for short visits which have been fruitful because the visitors have been able to base their studies on the resident scientists personal knowledge and understanding of the bushmen

The bushmen live in camps of 20 or more people the basis of which is an ex

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Table 1 Communities in which blood pressure does not rise with age

	Ethnic or socio economic group	Geographical location	Study
1	Africans	Kavirondo Kenya	Donnison 1929
2	Africans	Eastern Province Uganda	Williams 1941
3	Ponape Islanders	E Caroline Islands Micronesia	Murrill 1949
4	Pukapuka Islanders	N Cook Islands Polynesia	Murphy 1955 Hunter 1962 Prior et al 1968
5	Ethiopians	Ethiopia	ICNND 1958
6	Various communities	Papua and E New Guinea	Whyte 1958 Maddocks 1965 1967
7	Lower socio economic group men—industrial and rural	Delhi India	Padmavati 1959
8	Bushmen	Central Kalahari Botswana	Kaminer 1960
9	Abaiang Islanders	Gilbert Islands Micronesia	Maddocks 1961
10	Carajas Indians	Amazon basin N Brazil	Lowenstein 1961
11	Samburu, Rendille, Turkana } nomads	Northern Frontier Province Kenya	Shaper 1961 1967
12	Masai tribesmen	Tanzania	Mann et al 1964
13	Orang Asli	West Malaysia	Burns Cox 1970

tended family group Each camp is associated with a waterhole Lee[6] has found that about 70 per cent of food by weight is vegetable collected by the women A variety of nuts fruits roots bulbs and leaves are available varying with the season The most important food is the nut of the mongongo (manketti) tree *(Ricinodendron rautenenii)* because it is abundant keeps well and is rich in protein and fat [7] Meat is provided by some of the men who hunt with poisoned arrows

The bushmen have only a few basic possessions which they carry with them when they move they are therefore able to travel light Individuals move freely between camps and the camps move about five times a year During and after the wet season (November to March) there are pans of seasonal water out in the bush so that the bushmen can camp beside them and collect food in the surrounding area But as the pans dry up the bushmen return to the permanent waterholes at the end of the dry season they have to walk increasing distances to find food Some of the bushmen obtain milk occasionally from Bantu (Herero and Tswana) pastoralists who have settled in the area in the last 45 years A few bushmen work for the Bantu as herdsmen part of the year The bushmen have no alcohol but they smoke tobacco They have very little salt There are no deposits of salt in the area and the principal means of obtaining salt is to walk to Tsumkwe 30 miles away in South West Africa where the Administration has established a settlement for the !Kung bushmen on the South West African side of the border

The medical team made 3 visits to the Harvard camp each trip included 10 days work in the field The first visit was made in October, 1967 at the end of the dry season when it was hot and dry and food was scarce The second visit was in April May 1968 after the rains During that visit it was warm in the day and cool at night there were occasional pans of standing water in the area and some of the bushmen showed signs of malaria The third visit was made in July 1969 halfway through the dry season Though the nights were cold the days were sunny and quite warm out of the wind There was adequate food

The bushmen were seen in family groups Babies pregnant women the sick and the aged were all included in our first two visits A brief history was taken through an interpreter and each individual was examined with the subject lying down At the third visit we examined only adults for

Table II Mean blood pressures of bushmen in age and sex subgroups

Age (years)	15 19	20 29	30 39	40-49	50 59	60 69	70 83	Total numbers
Men (n)	120/75 (3)	124/75 (16)	1?0/75 (19)	116/75 (17)	118/7? (14)	113/67 (6)	117/66 (4)	— (79)
Women (n)	114/72 (5)	114/73 (17)	113/73 (13)	116/74 (17)	123/ 6 (9)	130/72 (8)	1?3/68 (4)	— (73)
Both sexes (n)	117/73 5	119/74 (33)	116 5/74 (3?)	116/74 5 (34)	1?0 5/74 (?3)	1?1 5/( ) 5 (14)	1?0/67 (8)	— (157)
Mean for both sexes	88 0	89 0	88 ?	88 3	89 5	86 8	84 7	

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whom we also recorded electrocardiograms (ECGs)[8] The ages of the bushmen have been carefully worked out using rank order ing and relating this to known historical events in the neighborhood The statisti cal technique for age determination was de eloped by Dr Nancy Howell Lee the demographer on the Harvard expedition and now at the Office of Population Re search Princeton N J The bushmen living within 10 miles of Dobe were brought to the ba e camp by truck for the examina tion Any who were ill were treated To examine the bu hmen at the extreme east of the area (Mahopa and Goshi) and all those living south of the Aha Hill (Nai Nai and Xoxgana) we took our equipment with us and drove to the bushman camps

Blood pressures were measured with the same mercury phygmomanometer (Baum anometer) throughout usually by Dr Trus well They were taken in the right arm with a cuff measuring 13 by 24 cm During the first two visits most of the subjects were examined on an improvised examination couch insi le the medical tent where it was a little cooler than out in the sun On the third visit the people were examined on a camp stretcher outside in the sun with the truck drawn up to provide shelter from the wind Conditions were unhurried and we tried to help the subjects feel relaxed Blood pre ures were measured during the course of a full medic l examination and the subject wa lying down with his family sitting nearby

Twenty four hour urine specimens were collected from 6 bushmen living at Dobe and from 2 controls (ourselves) in 1967 and from 4 of the same bushmen and from 3 controls in 1968 On each occasion the urines were collected on the eve of our return journey Aliquots (preserved with iodine in 1967 and with oxalic acid in 1968) were carried back with us by jeep and plane in a cool box and frozen as soon as we ar rived in Cape Town

Urinary sodium and potassium were measured by flame photometry with lith ium as internal standard and chloride was measured by potentiometric titration in an Aminco chloride titrator Creatinine was measured with alkaline picrate and nitrogen by Kjeldahl

Results

Blood pressures were measured in a total of 152 bushmen aged 15 to 83 years The study group was composed of 79 men and 73 women Measurements in 22 bushmen were taken on each of our 3 visits another 22 subjects were measured on 2 of the 3 visits The remaining 108 bushmen were examined only once For each bushman we used all the available measurements to obtain a best estimate of blood pressure which was therefore based on 2 or 3 re peated measurements at different seasons in 44 of the subjects and on a single mea surement in the re t (108 subjects) The individual blood pressure values were grouped by sex and decade and the mean values of the 14 subgroups are shown in Table II

In male bushmen systolic and diastolic pressures both showed a slight but definite downward trend with increasing age throughout adult life In the women the line joining decade mean systolic pressures rose by about 10 mm Hg to a higher step in the second half of life But their diastolic pressures stayed the same until the two oldest age groups, in which there was a slight drop

Combining the values for men and women (unweighted mean values in the third row of Table II), systolic pressures were about 3 mm higher in people over 49 years of age while diastolic pressures fell after the age of 59 Pulse pressures were 42 to 45 mm from ages 15 to 49 years and 52 to 53 mm from ages 60 to 83 years These trends are illustrated in Fig 1, against the curve of London blood pressures taken by Hamilton and associates[9] (1954) which is typical of Western developed communities The mean blood pressures (diastolic + ⅓ pulse pressure) for men and women combined condense all the results into a row of single figures at the bottom of Table II They show a remarkable constancy despite increasing age

In the 22 bushmen who were examined on all three visits the mean blood pressures were

October 1967	April May 1968	July 1969
117/73	126/75	111/64

The difference cannot be explained by observer variation, nearly all were taken by A S T The lower readings at the July (winter) visit were unexpected On this occasion subjects were examined outside in the winter sunshine and it is possible that they were more relaxed than when they were examined on their own inside the doctors tent on the two earlier visits

Table III shows the arm circumferences of the bushmen, arranged by sex and age The measurements were taken midway between the right elbow and shoulder in about half the subjects whose blood pressures were recorded The arm circumferences were at the lower end of the range in Western adults[10,11] In both sexes they

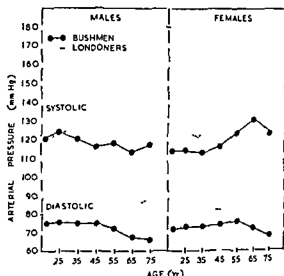


Fig 1 Bushmen s blood pressures with age compared with standard figures for a group from London (Hamilton and associates[9])

were a little higher between 30 to 49 years of age and a little lower in the very young and the very old

Almost all the bushmen examined were lean of delicate build and rather short Taking all ages together the men averaged 48 Kg (106 lb) in weight (unclothed) and were 161 cm (5 ft 3 in) tall (without shoes) At this height the ' desirable weight for small framed men is 53 5 to 57 2 Kg (118 to 126 lb) in the U S A[1] The women s mean height and weight were 150 cm (4 ft , 11 in) tall (without shoes) and 40 Kg (88 lb) (unclothed) compared with a "desirable weight range of 44 9 to 48 5 Kg (99 to 107 lb) for small framed women of the same height in the United States Unfortunately these 'desirable' weights are quoted for people wearing indoor clothes which might weigh 1 to 2 25 Kg The triceps skinfolds averaged 5 0 mm in the bushmen and 9 4 mm in the women

To see if there were any changes in weight with age in the two sexes weight/height ratios (metric) are shown in Table IV together with ratios calculated from average U S weights[12] All bushman values were low and there was little change with age except below the age of 20 and over the age of 69 years For comparison the weight/height index of young American men was 38 8 and it fell to 29 5 in the same men after 6 months semi starvation with the loss of 25 per cent of their body

Table III *Arm circumference of bushmen in cm*

Age (years)	*15 19*	*20 29*	*30 39*	*40 49*	*50 59*	*60 69*	*70-81*
Men	19 7	22 0	23 5	[illegible]4 2	2[illegible] 4	2[illegible] 2	17 8
(n)	(3)	(11)	(11)	(6)	(1)	(4)	(3)
Women	18 4	20 2	[illegible]1 4	21 4	19 0	21 8	16 6
(n)	(4)	(10)	(5)	(7)	(3)	(4)	(3)

Table IV *Weight/height ratios for bushmen compared with ratios calculated from average U S weights**

Age (*years*)	*15 19*	*20 29*	*30 39*	*40 49*	*50 59*	*60 69*	*70-83*
Bushmen†							
Men	24 [illegible]	30 0	30 4	31 1	28 8	30 2	24 2
Women	24 0	27 5	26 4	27 0	27 1	26 1	24 7
Average U S							
Men‡	34 0	38 7	40 4	41 3	41 6	40 7	—
Women	31 6	33 4	36 0	38 1	38 9	39 3	—

* R t os w calcul ted f m th f ll wi g f rmul $100 \times \frac{\text{weight (kg)}}{\text{height (m)}}$
† N mbe of b hm n each cell we e th sam as I T bl II
‡ C lculat d f m shoe 5 ft 4 in. in h ght and w men l shoe 5 ft 1 in he ght

weight as observed in the Minnesota experiment[13]

In the 24 hour urine specimens (Table V) the striking findings both in 1967 and 1968 were the low sodium and chloride content in the bushmen Sodium and chloride excretions of 30 mEq per day each would correspond to an NaCl intake of only 2 Gm per day The creatinine excretions look rather low in one or two of the bushman urine specimens suggesting that the collections were incomplete However the bushmen were smaller and weighed less than the controls When the creatinines are expressed per kilogram of body weight the bushman creatinines come to 83 per cent of the controls in 1967 and 86 per cent in 1968 Potassium nitrogen and magnesium excretions were not lower in the bushmen than in the controls

Discussion

There have been two previous observations of blood pressures in other groups of southern African bushmen Bronte Stewart and colleagues[14] mentioned mean values of 119/74 in men and mean values of 110/71 in women in northern South West Africa Pressures were only taken in 44 subjects and old people were probably under represented Kaminer and Lutz[1] measured blood pressures in 99 nomadic bushmen belonging to the Central Group of tribes living in the area south of Ghanzi Botswana The readings did not increase with age and none exceeded 140/90 Two complete bands of people were examined but ages could only be estimated by physical appearance

We have confirmed these findings in a larger group of separate bushmen whose ages have been worked out with a fair degree of accuracy There are different degrees to which populations can deviate from the standard Western blood pressure pattern exemplified by the curves for London presented in Fig 1 Maddocks[16] has introduced a useful classification In the Type 1 pattern mean systolic pressure

Table V Mean values (and ranges) of 24 hour urinary sodium and other constituents in bushmen and controls

Subjects	Year	n	Creatinine (Gm/day)	Sodium (mEq/day)	Chloride (mEq/day)	Potassium (mEq/day)	Nitrogen (Gm/day)	Magnesium (mEq/day)
Bushmen	1967	6	0 84 (0 56-1 40)	31 (8-48)	30 (7 77)	70 (31 93)	10 4 (5 [illegible] 14 9)	[illegible] 4 (0 3 9 6)
	1968	4	0 98 (0 54 1 41)	29 ([illegible] 64)	36 (5-[illegible]0)	103 (45-168)	10 6 (5 [illegible]-17 8)	
Controls	1967	2	1.36 (1 [illegible] & 1 4[illegible])	212 (1[illegible]9 & 215)	173 (132 & [illegible]15)	68 (5[illegible] & 84)	8 7 (6 4 & 11 0)	3 [illegible] ([illegible]1 & 4 [illegible])
	1968	3	1 4[illegible] (1 [illegible]-1 64)	147 (96-172)	121 (6[illegible] 154)	61 (43 75)	11 4 (10 1 13 1)	

rises considerably with age and diastolic pressure rises moderately In the Type II pattern, systolic pressure rises moderately but diastolic pressure does not rise In the Type III pattern, systolic and diastolic pressures both stay at the same low level throughout life and in the Type IV pattern both systolic and diastolic blood pressures decline with advancing age According to Maddocks classification the !Kung bushman males have a Type IV pattern and the women a Type II pattern When the two sexes and the diastolic and systolic pressures are combined the resulting mean blood pressures do not change with increasing age

There are five possible explanations for the bushmen s immunity from hypertension (1) low salt intake (2) lack of obesity (3) associated illnesses (4) freedom from the stresses of civilization, and (5) high magnesium intakes Taking them in reverse order, Verster[17] speculated that the relatively high serum magnesiums found in some central Kalahari bushmen[18] might be connected with their freedom from hypertension However these sera were not separated from red cells for about 2 days and neither Bernstein[18] nor we (Table V) found high urinary magnesiums in bushmen

There is no doubt that in some communities hypertension has appeared with "acculturation" [19, 20] But mental stress is only one of the changes that occur and it is the most difficult to quantify [21] Some isolated and peaceful communities have hypertension,[22, 4] although one would imagine they are not very stressful to live in

Tropical splenomegaly[25, 6] and chronic chest disease[26] have been associated with lower blood pressures than in the healthier members of the same communities A minority of the bushmen had splenomegaly but the spleens were usually not very large and appeared after the wet season, i e, in April, 1968 when we found blood pressures to be rather higher than at our other visits Some of the older bushmen showed evidence of chronic bronchitis but most of them appeared healthy on clinical examination We would not think that chronic infections play more than a minor part in keeping blood pressures low Maddocks and Vine[26] reached the same conclusion in New Guinea

The bushmen have thin arms and small amounts of adipose tissue Pickering Roberts and Sowry[10] calculated that to obtain the true direct blood pressure correction should be made for arm girth According to the table in their article, 10 mm Hg should be added to the bushmen s indirect systolic pressures and no correction should be made to the diastolic pressures This would not explain the absence of hypertension with increasing age because the bushmen s arm circumference stayed about the same throughout life More recent workers have found that the effect of arm girth per se is very small[11, 7] and that adiposity has a much closer association The bushmen have unusually small amounts of adipose tissue and (Table IV) show no middle aged spread Some of the other communities in Table I remain thin throughout life

Lastly our findings are consistent with Dahl s hypothesis[8] that populations habitually consuming less than 5 Gm of salt a day are relatively free of hypertension Some more recent between population comparisons[29] are also in keeping with this hypothesis Even if salt intake does not

determine which individuals become hyper tensive within a developed community the bushmen appear to eat a low salt diet which provides little more sodium than was used to *treat* essential hypertension[30] before oral diuretics became available

Summary

Blood pressures have been measured and sociological anthropometric medical and biochemical examinations have been made in an isolated group of !Kung bushmen in northern Botswana

Blood pressures were taken in 152 bush men of both sexes aged 15 to 83 years who were examined in family groups Systolic and diastolic pressures declined with in creasing age in the men The women showed a small rise of systolic pressure after the menopause but their diastolic pressure decreased slightly with age The mean blood pressure (diastolic + 1/3 pulse pressure) for men and women combined thus remained the same throughout life

Other communities whose blood pres sures do not increase with age are reviewed Of the possible explanations in the bush men, a low salt intake and a lack of obesity appeared to be important with relative freedom from mental stress an additional imponderable factor

We want to thank Professors I DeVore V Schrire and J E. Kench and Drs Nancy Howell Lee Henry Harpending Patricia Draper and John E. Yellen for their help in this work.

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Bushmen	1967	6	0.84 (0.56-1.40)	31 (8-48)	30 (7-77)	70 (31-93)	10.4 (5.2-14.9)	7.4 (6.3-9.6)
	1968	4	0.98 (0.54-1.41)	29 (2-64)	36 (5-70)	103 (45-168)	10.6 (5.5-17.8)	
Controls	1967	2	1.36 (1.29 & 1.42)	212 (179 & 245)	173 (132 & 215)	68 (52 & 84)	8.7 (6.4 & 11.0)	3.2 (2.1 & 4.2)
	1968	3	1.42 (1.23-1.64)	147 (96-172)	121 (62-154)	61 (43-75)	11.4 (10.1-13.1)	

rises considerably with age and diastolic pressure rises moderately In the Type II pattern, systolic pressure rises moderately but diastolic pressure does not rise In the Type III pattern, systolic and diastolic pressures both stay at the same low level throughout life, and in the Type IV pattern both systolic and diastolic blood pressures decline with advancing age According to Maddocks' classification the !Kung bushman males have a Type IV pattern and the women a Type II pattern When the two sexes and the diastolic and systolic pressures are combined the resulting mean blood pressures do not change with increasing age

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Cardiomyopathy without cardiomegaly in alcoholics

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Clinical and experimental evidence in recent years has prompted physicians to recognize the entity of alcoholic cardiomyopathy with increasing frequency.[1-6] There is evidence that acute administration of alcohol to normal humans produces myocardial cellular damage as evidenced by loss of intracellular constituents such as potassium, phosphates, and enzymes with associated impairment of hemodynamic function.[4,5] Despite the wide prevalence of alcoholism in this country, cardiac symptoms in an alcoholic patient have often been ignored unless obvious clinical, electrocardiographic (ECG), or radiologic evidence of cardiomegaly or arrhythmias is present. Clinicians often wait until cardiac enlargement is obvious prior to entertaining the possibility of myocardial involvement. We have attempted to define an earlier stage of this syndrome and we therefore studied a group of alcoholic patients with mild functional impairment who otherwise presented with no increase in cardiothoracic ratio on chest x-ray and who had normal ECG's.

Materials and methods

Hemodynamic studies were performed in nine patients with a history of alcoholism ("moonshine drinking") of 5 to 25 years duration. They were selected from those who had presented to the outpatient clinic because of cardiac symptoms which could not readily be explained. Others had noncardiovascular ailments such as dermatological problems with no evidence of systemic involvement. There was no evidence of gross nutritional deficiency or anemia (hematocrit 45 ± 2) in these patients. Further, all patients were studied after approximately three weeks of abstinence from alcohol while ingesting a regular hospital diet.

No patient had a history of delirium tremens or required sedatives or tranquilizers. Abnormal cardiovascular physical findings such as cyanosis, persistent splitting of S_2, abnormal parasternal lifts or apical thrusts were not present. Chronic lung disease was excluded clinically and also when it was indicated with pulmonary function tests when chest x-ray suggested minor parenchymal abnormalities or the presence of infiltrates. Liver and kidney function studies including Bromsulphalein and creatinine clearance were normal in all patients. Retinal vessels were normal. There were no histories suggesting recent viral illness. No patient had visited South

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Fig. 1. Chest x-ray of patient No. 3 (W. L.)



Fig. 2. Chest x-ray of patient No. 1 (N. K.)

America or other areas where Chagas' disease is endemic.

Presenting symptoms in these patients were of a mild degree. Five had fatigue, four had dyspnea on exertion, and four experienced nonspecific chest pain. Physical examination revealed the presence of third heart sounds in four patients and fourth heart sounds in five patients. Abnormal cardiac function was suspected in the asymptomatic because of the presence of findings such as a third or fourth heart sound. Although there were no clear-cut indications for diagnostic catheterization, the majority of these patients had volunteered for another study[9] from this laboratory. In some patients, e.g., Nos. 5 and 9, no cardiac dysfunction was expected on clinical grounds. In these and the others the compelling reason for investigating these patients was the need to demonstrate whether a history of alcoholism alone is enough to anticipate abnormal cardiac function.

All patients had standard "cardiac series" with barium-filled esophagus in four views. Cardiac silhouette, chamber size, pulmonary vascularity, etc., were assessed to rule out lesions suggesting either congenital or acquired diseases such as shunts and valvular stenosis. All but one patient had normal cardiothoracic ratios (Table I, Figs. 1 and 2). Because of their ages (mean age 41 ± 2 yr.) a relatively low prevalence of coronary heart disease was expected. Further, no history suggestive of coronary artery disease was obtained, and standard twelve lead electrocardiography and exercise testing gave no evidence for it. Nevertheless, those with chest pains, although atypical for angina pectoris, underwent selective coronary arteriography (Table I).

Right and left heart catheterization was performed under mild barbiturate sedation. The maximal rate of left ventricular pressure rise (MRPR) was recorded with an RC differentiating unit available in the multi-channel recorder (Electronics for Medicine DR8). Catheters (80 cm. 7 F NIH) were of the shortest length with maximum diameter and were directly attached to the Statham strain gauges. Comparison of the conventional fluid-filled catheter manometer system with a Statham SF₁ catheter tip transducer has revealed that the former is linear up to dp/dt maximum of 2,500 mm. Hg per second and exhibits a small (5 per cent) overestimate between 2,500 and 3,000 mm. Hg per second.[10]

Further control data (Fig. 5) were ob-

Table I Descriptive data in nine alcoholic patients with normal cardiothoracic ratios

Patient	Age (yr)	BSA* (M²)	NYHC†	CTR‡	Coronary arteriograms§
1 N K	46	2.07	1 A	0.45	—
2 D S	48	1.86	2 B	0.53	—
3 W L	39	1.8[illegible]	2 C	0.46	N
4 W C	3[illegible]	1.6[illegible]	[illegible] C	0.44	—
5 H S	47	1.7[illegible]	1 A	0.43	N
6 I T	36	1.64	2 B	0.45	N
7 W I	5[illegible]	2.30	1 A	0.48	N
8 I H	49	1.8[illegible]	[illegible] C	0.4[illegible]	N
9 Hy St	37	1.67	1 A	0.46	N
Mean	4[illegible]	1.83		46	
Standard error	2.3	0.07		00	

*BSA = Body surface area.
†NYHC = New York Heart Classification.
‡CTR = Cardiothoracic ratio.
§Coronary arteriogram N = Normal

tained in the same fashion by the same personnel. Cardiac outputs and left ventricular volumes were measured in duplicate using the indicator dilution method.[11] Significant shunts were also ruled out in this fashion. The presence of valvular regurgitation was essentially ruled out by dye dilution techniques and when indicated by angiography. Pericardial disease was excluded clinically and also at catheterization.[12,13]

An index of contractility[14] was employed to examine left ventricular performance. Briefly, this index is expressed as MRLR/MII 2πr. MRLR represents the maximum rate of left ventricular pressure rise, MII the maximum isovolumetric pressure, and 2πr represents the circumferential fiber length of the left ventricle which helps to normalize the index for hearts of different sizes. Adjustments in the fiber length 2πr were calculated assuming that the left ventricle was a sphere at the end of the systolic isovolumetric period deriving the radius(r) from the end diastolic volume measured by indicator dilution. MRPR and MII (aortic diastolic pressure) were obtained simultaneously by means of two catheter systems, one in the left ventricle and the other in the aortic root. Estimates of LV volumes were done in duplicate within five minutes of the appropriate pressure recordings. Contractility indices obtained in this fashion were compared with normals from this laboratory.[14]

Results

A summary of the hemodynamic data is shown in Tables I and II. The mean cardiac output was 2.56 ± 0.21 L per minute per mole which is significantly lower ($p < 0.05$) than expected for patients of this age group (3.19 ± 0.29 L per minute per mole²).[1] The left ventricular end-diastolic volume was normal in 7 out of 9 patients; in one patient it was slightly increased and in the other it was moderately increased. Left ventricular end diastolic pressures were elevated in all but two patients. It is noteworthy that two patients who were asymptomatic had decreased cardiac indices and elevated left ventricular end-diastolic pressures (patients Nos 1 and 5). In patients whose coronary arteries were selectively opacified (Table I) no angiographic abnormalities were detected (e.g. Figs 3 and 4, patient No 6). The calculated left ventricular contractility index was 0.67 ± 0.05 as compared to a normal of 1.27 ± 0.09 in our laboratory, a significant difference (Fig 5).

Discussion

The growing number of alcoholic subjects with myocardial disease in the absence of a readily definable nutritional deficiency has increased acceptance of the concept that

Table II Hemodynamic data in nine alcoholic patients with normal cardiothoracic ratios

Patient no	*Ra** (*mm Hg*)	*RVED* (*mm Hg*)	*RVS* (*mm Hg*)	*PAS* (*mm Hg*)	*PAD* (*mm Hg*)	*PAM* (*mm Hg*)	*CI* (*L/M²*)
1	4	10	35	35	10	21	1 97
2	8	12	35	35	12	22	2 35
3	5	10	38	38	15	22	3 07
4	4	4	40	40	11	21	1 63
5	5	5	29	29	8	17	2 27
6	3	9	24	24	9	16	2 14
7	5	5	28	28	10	18	2 84
8	5	14	38	38	21	26	3 67
9	11	19	32	32	19	24	3 2
Mean	5 5	9 7	33 2	32 3	12 7	20 7	2 56
Standard error	0 8	1 6	1 7	1 7	1 5	1 09	0 21

*Abbreviations Ra = right atrium RVED = right ventricular end diastolic pressure RVS = right ventricular systolic pressure PAS index SVI = stroke volume index EDVI = end diastolic volume index *MRLR = maximal rate of left ventricular pressure rise* FF aortic diastolic pressure

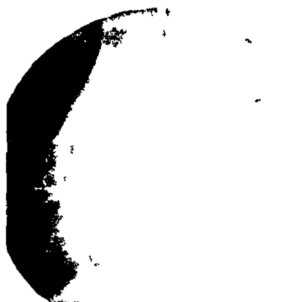


Fig 3 *Selective coronary angiogram of the right* coronary artery of patient No 6 (F T) The vessel is normal in caliber and distribution



Fig 4 Selective coronary angiogram of the left coronary artery of patient No 6 (F T) The vessel is normal in caliber and distribution

alcohol itself is able to produce chronic functional myocardial impairment However *much of the published work on the* clinical recognition of alcoholic cardiomyopathy[2,4] stresses that cardiac enlargement is a prerequisite for its diagnosis The majority of alcoholic patients with en*larged hearts arrhythmias* and recurrent heart failure have a poor prognosis The need to recognize this entity prior to the development of severe and irreversible myocardial damage is obvious Moreover many patients with normal ECG s and no

apparent cardiac enlargement are often suspected to be neurotic and their symptoms labelled functional While this may be true in some the present data indicate that this is not necessarily so The cardiac outputs were significantly lower than predicted for patients of this age group[1] The abnormally high mean left ventricular end *diastolic pressures in this group in the pres*ence of normal mean left ventricular end diastolic volume reflect a significant reduc*tion in compliance of this chamber A large* end diastolic volume was obtained for

1 / m 84
5 mb 1

SVI (ml/M²)	EDVI (ml/M²)	MRPR (mm Hg/sec)	EF	CoI	LVS (mm Hg)	LVED (mm Hg)	AOD (mm Hg)
76	67	935	0 41	0 64	112	14	74
39	108	1 150	0 36	0 55	165	15	97
49	140	935	0 34	0 50	141	14	77
28	60	1 164	0 46	0 63	165	15	98
35	64	1 589	0 53	0 99	148	17	85
75	58	1 041	0 44	0 58	148	10	99
41	83	1 300	0 52	0 71	108	11	87
37	61	1 360	0 67	0 89	174	28	81
38	83	1 077	0 46	0 60	130	18	85
35	80	1 166	0 46	0 67	137	16	85
[illegible]	9	77	0 07	0 05	6	1 7	2

r n ty tl ry systol pressure PAD = p lm ry rte y d t l pressure PAM = p lm nary artery mea p e ure CI = ca dia tio l actio C I = tra til ty nd LVS – l ft v cular systol p essu e LVED = left e tricula end-d a tolic p ssure AOD =

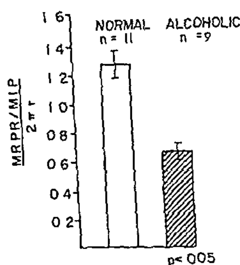


Fig 5 Left ventricular contractility index for normal and patient with alcoholic cardiomyopathy

patient No 3 in the face of a normal cardiothoracic ratio This x ray measurement is of course an insensitive method of predicting chamber volumes We have also demonstrated evidence of decreased left ventricular function and depressed contractility in these patients even in the absence of ECG abnormalities or obvious radiological changes. Early recognition of this entity appears important in order to attempt timely rehabilitation Although cardiac catheterization may not be clearly indicated in the majority evaluation of cardiac performance at an early stage of the disease seems desirable Noninvasive techniques of measuring cardiac performance such as measurement of systolic time intervals [16,17] echocardiography [18] and exercise stress testing may be useful in the initial assessment and follow up With this in view we are at present assessing the value of serial measurement of systolic time intervals and exercise stress testing in detecting left ventricular functional impairment in alcoholic patients

Summary

For obvious reasons it is important to recognize alcoholic cardiomyopathy early in its natural history Hemodynamic studies were performed in nine patients with normal ECG s and normal cardiothoracic ratios on chest x rays Findings were elevated mean LV end-diastolic pressure low mean cardiac output and depressed myocardial contractility Thus true functional cardiac impairment may exist in these patients even prior to the development of abnormal clinical parameters such as cardiomegaly

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Rules for the diagnosis of visceral situs, truncoconal morphologies, and ventricular inversions

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At the present time there is great confusion of concepts with respect to visceral situs,[1-4] the positions of the heart,[2,3,5,7,10] ventricular inversions,[2,11] and the truncoconal morphologies,[2,11,13] all of which has led to the creation of a vast nomenclature, most of which is not correct.[1,5,11,14,15] It is our belief that on the basis of embryologic facts[16-18] the basic rules may be established and these will always apply. They are most useful for the anatomic and radiologic diagnosis of these entities, both in their simple forms as well as in the complex varieties when they are associated with malformations of the atrioventricular canal, such as persistence of the common atrioventricular canal, double inlet of the ventricles, and atresia of the atrioventricular orifices.

Diagnosis of the visceral situs

A visceral situs is the position and the reciprocal spatial relation of the viscera within a system of symmetry.

There are two main types of situs: solitus and inversus. Although heterotaxias constitute a visceral situs, they will not be studied in this paper because, due to their anatomic and embryologic features, they do not conform to the rules which apply to situs solitus and situs inversus. The diagnosis of a situs is made by determining the position of those internal organs which do not change their position in space in an isolated fashion but rather remain permanently related to the type of situs of which they are part. Furthermore, they show features which permit the identification of the right and left structures.

The abdominal viscus which should be selected for the diagnosis of a situs is the liver, since it has the features previously mentioned, while the stomach, the intestine, and the spleen may change their spatial position independently of the situs of which they form part due to isolated malformations and malrotations of these organs.

The atria are the only chambers of the heart which serve the purpose of diagnosing a given situs because they do not vary their position independently of the situs and because the anatomical features of the right atrium are different from those of the left

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atrium and this permits their differentiation The anatomically right atrium* has internal structures which identify it and it always receives the suprahepatic portion of the inferior vena cava†, its atrial appendage is triangular with smooth borders while the anatomically left atrium has a specific internal architecture and possesses a smaller appendage than that of the right atrium, it exhibits a narrow neck at its base and its edges are irregular

The superior vena cava is not a structure by which the diagnosis of an anatomically right atrium can be made This is because this structure originates from the system of the anterior cardinal veins and the common cardinal veins, which are bilateral and symmetric vessels in the embryo which may develop (1) normally persisting as the superior vena cava which drains into the anatomically right atrium while the opposite vein disappears, or (2) abnormally, persisting as both superior venae cavae or in the disappearance of the superior vena cava which normally drains into the anatomically right atrium while the opposite superior vena cava may drain directly into the anatomically left atrium or through the coronary sinus into the anatomical right atrium The pulmonary veins are not useful to identify the anatomical left atrium either due to the fact that there may be a total anomalous pulmonary venous connection

The diagnosis of a situs is made by locating the spatial position of the major lobe of the liver and the suprahepatic portion of the inferior vena cava together with the anatomical right atrium (hepato cavo atrial concordance) The radiological diagnosis of the anatomical right atrium is made by locating the suprahepatic portion of the inferior vena cava (Figs 1 to 5)

There is no such thing as atrial inversion because the position of the atria is fixed for each situs and therefore these chambers are the cardiac structures which determine the situs[19] On the contrary there are two types of atrioventricular relations for each situs (Fig 1, *B* and *C* and Fig 2, *B* and *C*), depending on the concordant or discordant position of the ventricles with respect to the situs[19] (Figs 3 4, and 5)

The diagnosis of visceral situs solitus is established when the major lobe of the liver, the suprahepatic *portion of the inferior vena cava*, and the anatomically right atrium are placed *on the right side* independently of the position of the remaining viscera (*Figs 1A 3A and B 4A and B, and 5A and B*)

The diagnosis of visceral situs inversus is established when the major lobe of the liver, *the suprahepatic portion of the inferior vena cava*, and the anatomically right atrium are placed *on the left side* constituting therefore a mirror image of situs solitus (*Figs 2A, 3C and D, and 4C and D*)

The direction of the cardiac apex may have three distinct positions for each visceral situs left sided apex middle-placed position of the apex, or right sided apex The nomenclature for the right or left position of the apex relates its direction with the visceral situs[20] A normally placed heart is one in which the cardiac apex is directed to the left in a situs solitus (Fig 1 *J*) This same direction of the cardiac apex in a heart which forms part of a situs inversus is designated as levoversion or levocardia (Fig 2 *L*)

The heart with a right sided apex in a situs solitus is best designated as dextroversion (Fig 1 *L*) while that heart with an apex to the right in a situs inversus is best designated as mirror image dextrocardia (Fig 2 *J*) The medial position of the cardiac apex is called mesocardia independently of the visceral situs of which it forms part (Figs 1*K* and 2*K*)

Diagnosis of truncoconal morphologies

The truncus of the embryonic heart gives origin to the ascending aorta and the trunk of the pulmonary artery and its conus forms the infundibulum of the right and of the left ventricles[17] The study of the different truncoconal morphologies should be done in the following order (1) one should specify

*The anatomically right atrium is characterized by the presence of the crista terminalis which separates the smooth (sinus) portion from the pectinate muscles The latter begin in this crista and direct themselves toward the apex of the atrial appendage The anatomically left atrium is smooth and its atrial appendage has a fine network of [illegible]

†When there are anomalies of the inferior vena cava the constantly present segment is the suprahepatic portion which is the oldest portion of the vessel both *ontogenetically* and phylogenetically since it originates from the vitelline veins

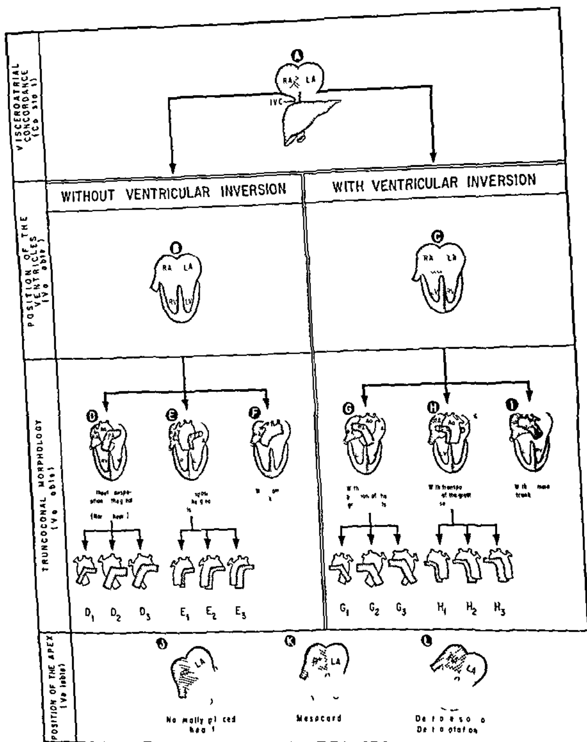


Fig 1 Diagrams representing the typical atrial position in situs solitus the atrioventricular relations that of the great arteries with each other and those of these arteries with the ventricles The different directions of the cardiac apex are depicted *RA* = anatomically right atrium *LA* = anatomically left atrium *IVC* = inferior vena cava *RV* = anatomically right ventricle *LV* = anatomically left ventricle *Ao* = aorta *PA* = pulmonary artery *CT* = common trunk.

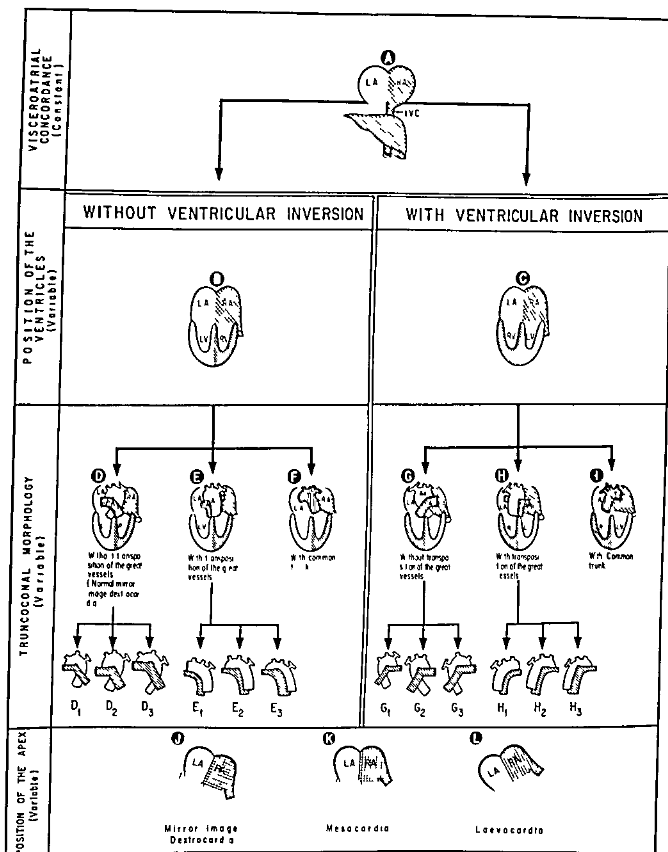


Fig 2 Diagrams representing the characteristic atrial position in situs inversus, the atrioventricular relation, those of the great arteries with each other and those of these arteries with the ventricles. The different directions of the cardiac apex are depicted. *RA* = anatomically right atrium; *LA* = anatomically left atrium; *IVC* = inferior vena cava; *RV* = anatomically right ventricle; *LV* = anatomically left ventricle; *Ao* = aorta; *PA* = pulmonary artery; *CT* = common trunk.

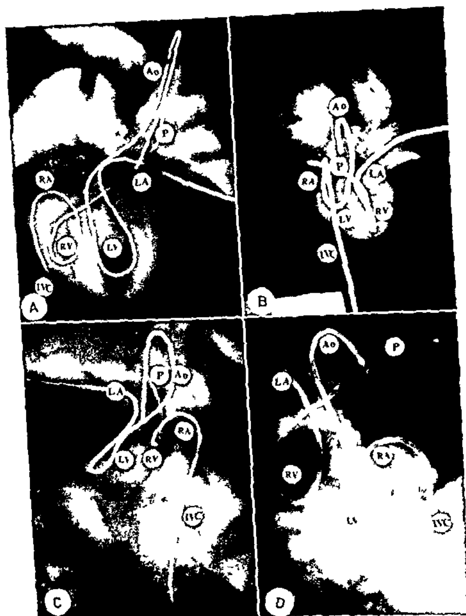


Fig. 3 *A* through *D* Postmortem radiological studies with catheters placed in the cardiac chambers and the great arteries. Frontal view. Identification of the ventricular cavities by means of the spatial relation of the two great arteries between themselves. Panels *A–D* correspond *to hearts with* great arteries crossing each other (without transposition of the great arteries) in space. *A* Normal heart in situs solitus. *B* Ventricular inversion in situs solitus without transposition of the great arteries. *C* Normal heart in situs inversus (mirror image dextrocardia). *D* Ventricular inversion in situs inversus without transposition of the great arteries (mirror image dextrocardia). Notice that in every case the pulmonary artery (*P*) crosses the aorta (*Ao*) ventrally, which means that there is no transposition of the great arteries. In Panels *A* and *D* the catheter placed in the pulmonary artery is directed from right to the left, indicating that the anatomically right ventricle (*RV*) is placed on the right. In Panels *B* and *C the catheter in the* pulmonary artery is directed from left to right, pointing out that the anatomically right ventricle is placed on the left. The portion of the catheter bearing the letters IVC shows that the inferior vena cava *enters the anatomically* right atrium (*RA*) (sign of situs solitus) in Panels *A* and *B*. In Panels *C* and *D* it enters the anatomically right atrium placed on the left, the characteristic feature of situs inversus. *LA* = anatomically left atrium. *LV* = anatomically left ventricle.

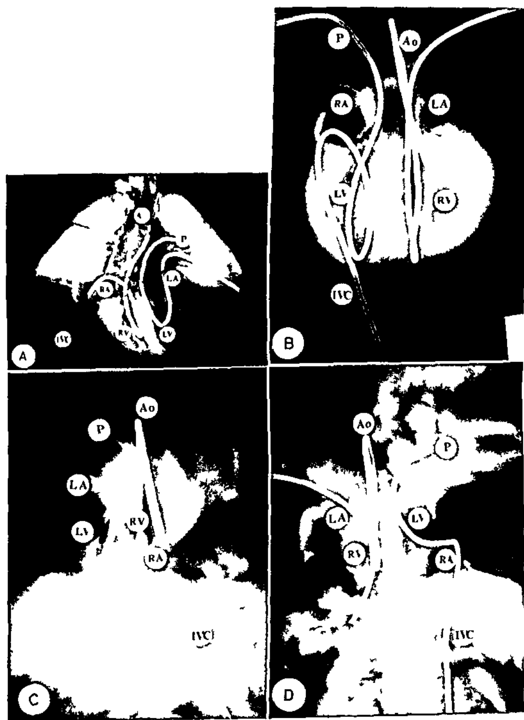


Fig. 4. *A* through *D*. Postmortem radiological studies with catheters placed in the cardiac chambers and the great arteries. Frontal views. Identification of the ventricular chambers by means of the spatial relation of the two great arteries between themselves. Panels *A–D* illustrate hearts with transposition of the great arteries. *A*, Transposition of the great arteries in situs solitus without ventricular inversion. *B*, Transposition of the great arteries in situs solitus with ventricular inversion. *C*, Transposition of the great arteries in situs inversus without ventricular inversion (mirror image dextrocardia). *D*, Transposition of the great arteries in situs inversus with ventricular inversion (mirror image dextrocardia). Notice that in every case both arteries are parallel and this indicates that there is transposition of the great vessels. In Panels *A* and *D* the catheter placed in the aorta (*Ao*) is parallel and placed on the right side of the catheter in the pulmonary artery (*P*), which indicates that the anatomically right ventricle (*RV*) is placed on the right. In Panels *B* and *C* the catheter placed in the aorta is parallel and placed on the left of the catheter within the pulmonary artery, indicating that the anatomically right ventricle is placed on the left side. *RA* = anatomically right atrium; *LA* = anatomically left atrium; *LV* = anatomically left ventricle; *IVC* = inferior vena cava.

the presence of one or two vessels arising from the heart (2) the spatial relations of the great arteries between themselves should be determined (3) the size of each of the arteries should be given with respect to the size of normal arteries and (4) the relations of these arteries with the ventricles should be established

1 *Define whether there are one or two arteries arising from the heart* When one artery emerges from the heart the diagnosis of persistent truncus arteriosus is made and this should be differentiated from pulmonary atresia with biventricular aorta in its two varieties—with transposition of the great arteries or without transposition of the great arteries[1] (extreme tetralogy of Fallot) In the case of a truncus arteriosus both branches of the pulmonary artery arise directly from this trunk or by way of a vessel which embryologically is the cephalic portion of the pulmonary artery There should not be a fibrous cord representative of this artery In the angiographic study of pulmonary atresia with biventricular aorta the branches of the pulmonary artery are filled through a patent ductus arteriosus since the trunk of this artery is represented by a fibrous cord

2 *Establishment of the spatial relations of both vessels with each other in order to determine the three truncoconal morphologies[19] which may be present* (a) straight and parallel great arteries in the sagittal plane therefore anterior aorta and posteriorly placed pulmonary artery (*transposition of the great arteries*) (b) parallel arteries in the frontal plane (partial distortion) and (c) crossed arteries in space therefore anteriorly placed pulmonary artery at its origin with respect to the aorta This latter group includes the normal pedicle and that of every congenital cardiopathy with two great arteries (with the exception of transposition of the great arteries in all of its varieties) and the partial distortions among which is the Taussig Bing complex

3 *Determine the size of the great arteries with respect to the normal size* The pulmonary artery may exhibit a larger than normal caliber such as seen in atrial septal defect or it may be narrow as seen in the tetralogy of Fallot The aorta may exhibit the same variations in size seen in the pulmonary artery For example there is a variety of Eisenmenger s complex with a narrow aorta smaller than normal

4 *Establishment of the relations of the great arteries with the ventricles* The anterior infundibulum always corresponds to the anatomically right ventricle, while the posterior infundibulum belongs to the anatomically left ventricle When there is transposition of the great arteries the aorta is the anterior artery and therefore it arises from the anterior infundibulum which belongs to the anatomically right ventricle while the pulmonary artery arises from the posterior infundibulum which belongs to the anatomically left ventricle (Figs 6 *B* and 7 B_2) However if there is a concomitant lateral position (dextroposition) the pulmonary artery will continue to be the posterior vessel and it will override the interventricular septum or else it will arise from the anatomically right ventricle behind the aorta[29] (Figs 6 A_2 and 7 A_2) If the great arteries cross each other in space the anterior vessel which is the pulmonary artery will arise from the anterior infundibulum belonging to the anatomically right ventricle and the aorta will arise from the posterior infundibulum belonging to the left ventricle (Fig 6 B_1 and Fig 7 B_1) But if there is in addition a dextroposition the aorta will continue to be a posterior vessel and it may override the interventricular septum or else it may arise from the anatomically right ventricle behind the pulmonary artery[29] (Fig 6 A_1 and Fig 7 A_1)

Anatomical and spatial identification of the ventricles*

The spatial identification of the ventricles is important to diagnose the normal or inverted position in each of the situs that is the atrioventricular concordance or discordance in a given situs For instance the normal position of the ventricles for situs *solitus* is the situation in which the anatomically right ventricle is placed on the

* The nat mically right v t le I th c hi h exh bit the ... iat of rav triculans, tl a t par llary m scle the mod rat ba d d th trabecul t l septal rf e l d pe d tly f tl e po t of tl ca ty sp ce The an t cally left t ule th t w l l la k i t su p a l cul q l t grou ps of p i ll ry m scl a d a ooth septal surf ce the ppe t o th d of th septum a l t bec lated the lo e th d l d pe d tly of the positio of th b mbe in sp ce

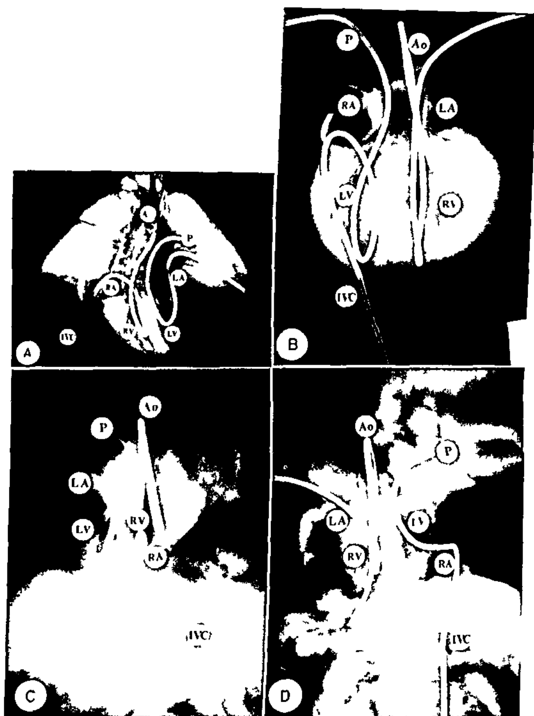


Fig. 4. *A* through *D*, Postmortem radiological studies with catheters placed in the cardiac chambers and the great arteries. Frontal views. Identification of the ventricular chambers by means of the spatial relation of the two great arteries between themselves. Panels *A–D* illustrate hearts with transposition of the great arteries. *A*, Transposition of the great arteries in situs solitus without ventricular inversion. *B*, Transposition of the great arteries in situs solitus with ventricular inversion. *C*, Transposition of the great arteries in situs inversus without ventricular inversion (mirror image dextrocardia). *D*, Transposition of the great arteries in situs inversus with ventricular inversion (mirror image dextrocardia). Notice that in every case both arteries are parallel and this indicates that there is transposition of the great vessels. In Panels *A* and *D* the catheter placed in the aorta (*Ao*) is parallel and placed on the right side of the catheter in the pulmonary artery (*P*), which indicates that the anatomically right ventricle (*RV*) is placed on the right. In Panels *B* and *C* the catheter placed in the aorta is parallel and placed on the left of the catheter within the pulmonary artery, indicating that the anatomically right ventricle is placed on the left side. *RA* = anatomically right atrium; *LA* = anatomically left atrium; *LV* = anatomically left ventricle; *IVC* = inferior vena cava.

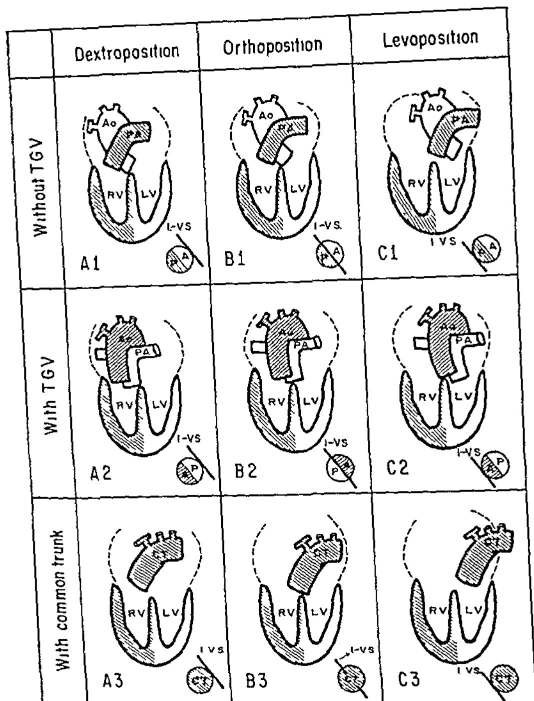


Fig 6 Lateral positions in situs solitus without ventricular inversion or in situs inversus with ventricular inversion. Diagrams representing the different truncoconal morphologies as a sign for the identification of the spatial position of the ventricular chambers In the case of crossed arteries the direction from right to left of the pulmonary artery (*PA*) indicates that the anatomically right ventricle (*RV*) is placed on the right in the case of transposed arteries the right sided position of the aorta (*Ao*) with respect to the pulmonary artery indicates the right sided position of the anatomically right ventricle The direction from right to left of the common trunk (CT) indicates that the anatomically right ventricle is placed on the right side *LV* = anatomically left ventricle *TGV* = transposition of the great vessels

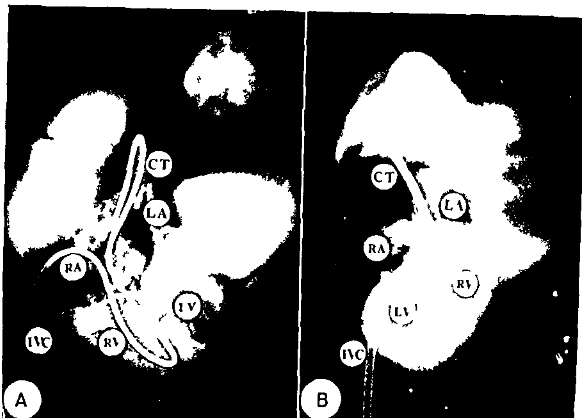


Fig 5 *A* and *B* Radiologic postmortem studies with catheters placed in the cardiac cavities and the great arteries Frontal views The two pictures correspond to hearts with a common trunk Identification of the ventricular chambers by means of the direction of the common trunk *A* Common trunk in situs solitus without ventricular inversion *B* Common trunk in situs solitus with ventricular inversion Notice that in both cases *a single vessel arises from the heart In Panel A the common trunk (CT) is directed from right to left* indicating that the anatomically right ventricle (*RV*) is placed on the right In Panel *B* the direction of the the common trunk from left to right testifies to the fact that the anatomically right ventricle is placed on the left side *RA* = anatomically right atrium *LA* = anatomically left atrium *LV* = anatomically left ventricle *IVC* = inferior vena cava

right connecting with the anatomically right atrium placed on the same side[19] (Figs 1*B*, 3*A* 4*A* and 5*A*) and the abnormal position (ventricular inversion or atrioventricular discordance) for this situs is the anatomically left ventricle placed on the right side and connecting with the anatomically right atrium placed on the right (normal atrial position for situs solitus)[19] (Figs 1*C* 3*B* 4*B* and 5*B*)

The normal position of the ventricles in a situs inversus is a situation in which the anatomically left ventricle is placed on the right and is therefore connected with the anatomically left atrium placed on the right[19] (Figs 2*B*, 3*C*, and 4*C*) The abnormal position of the ventricles (ventricular inversion or atrioventricular discordance for this situs) is that in which the anatomically right ventricle is placed on the right and connects with the anatomically left atrium placed on the right (normal atrial position for situs inversus)[19] (Figs 2*C* 3*D*, and 4*D*) The nomenclature of "ventricular situs solitus" or "situs inversus"[3] is unacceptable because the normal or inverted position of these chambers depends on the situs of which they are a part Thus the anatomically right ventricle on the right side is the normal position in situs solitus but it is an abnormal situation—i e ventricular inversion if it is within the context of a situs inversus (compare Figs 1*B* and 3*A* with Figs 2*C* and 3*D*)

In order to determine the position of the ventricles we have first to place them in space and then integrate them within the situs of which they are a part and which has been previously diagnosed *The spatial position of the ventricles is determined by utilizing the elements given by the analysis of the truncoconal morphology The integration of*

the ventricles within a given situs is established by correlating the position of the ventricles with the anatomically right atrium the suprahepatic portion of the inferior vena cava and the major lobe of the liver which are the elements that identify the situs

The designation of d loop[2] to establish the position of the ventricles is erroneous from the semantic point of view because it designates the position of a specific anatomic structure of the fetal and postnatal heart such as the ventricles using a nomenclature which is meant for the identification of a type of characteristic cardiac morphology which is only present in an embryonic stage of the development of this organ [16] On the other hand this nomenclature has no significance if it is not referred to a given situs For instance the d loop in a situs inversus is a ventricular inversion since the anatomically left atrium placed on the right connects with the anatomically right ventricle placed on the right (Figs 2C 3D and 4D) In situs solitus on the contrary it means that there are normal atrioventricular relations since the anatomically right atrium placed on the right connects with the anatomically right ventricle also placed on the right (Figs 1B 3A 4A and 5A) In the same manner the l loop in situs inversus established the normal atrioventricular relations for this situs since the anatomically left atrium placed on the right connects with the anatomically left ventricle placed on the right (Figs 2B 3C and 4C) and in situs solitus it is a ventricular inversion since the anatomically right atrium placed on the right connects with the anatomically left ventricle placed on the right (Figs 1C 3B and 4B)

The rules for the diagnosis of the spatial position of the ventricles are conditioned by the type of truncoconal morphology of the hearts– great arteries which cross in space (without transposition of the great arteries) transposition of the great arteries or truncus arteriosus communis

1 *Great arteries crossed in space* When the two great arteries are crossed in space the pulmonary artery is always the anterior vessel and therefore it arises from the anatomically right ventricle[27] In order to make sure of the position of this ventricle in space it is necessary to determine the direction of the pulmonary artery The hemodynamic and angiocardiographic diagnosis is made by means of a lateral x ray plate in order to demonstrate that the pulmonary artery is anterior with respect to the aorta and a posteroanterior (frontal) x ray film in order to determine the direction of the pulmonary artery If this artery goes from right to left the anatomically right ventricle is placed on the right (Figs 1D 2G 3A and 3D) if it is directed from left to right the anatomically right ventricle is placed on the left (Figs 1G 2D 3B and 3C) Furthermore in both directions of the pulmonary artery the valvular plane is higher than the plane of the aorta

2 *Transposition of the great arteries* In transposition of the great arteries the aorta is the anterior vessel and therefore it arises from the anterior infundibulum which belongs to the anatomically right ventricle[2] this element by itself does not permit us to ascertain the spatial position of this ventricle so that it becomes necessary to establish the relation of the pulmonary artery with respect to the aorta The hemodynamic and angiocardiographic diagnosis is done by means of a lateral x ray film in order to demonstrate that the aorta is anterior with respect to the pulmonary artery and a frontal x ray film in order to determine the position of the aorta with respect to the pulmonary artery If the aorta is on the right side of the pulmonary artery the anatomically right ventricle is on the right side (Figs 1E 2H 4A and 4D) and if the aorta is on the left side of the pulmonary artery the anatomically right ventricle is on the left side (Figs 1H 2E 4B and 4C) In transposition of the great arteries the level of the valve cusps of the aorta is always higher than that of the pulmonary artery

The designation of d transposition[2] (anterior aorta to the right of the pulmonary artery which indicates that the anatomically right ventricle is placed on the right) and that of l transposition[2] (anterior aorta placed on the left side of the pulmonary artery which indicates that the anatomically right ventricle is placed on the left side) has no meaning unless one relates it

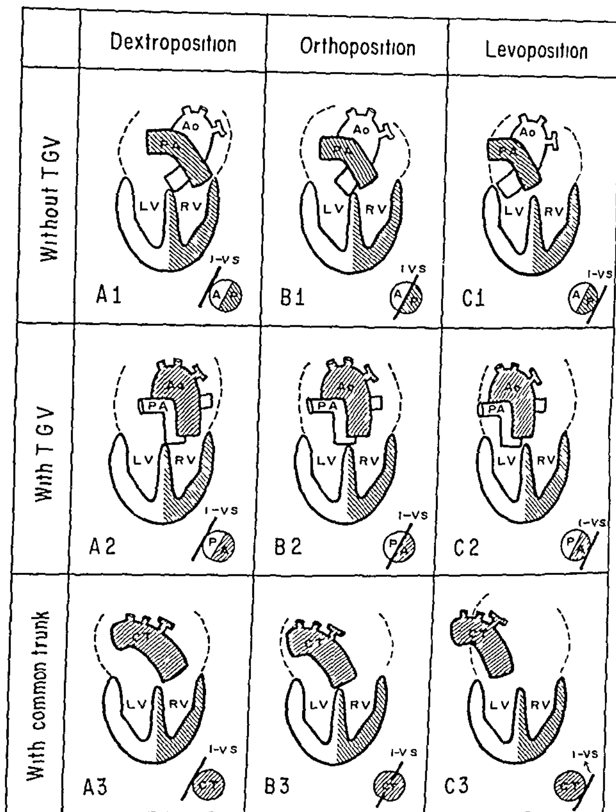


Fig. 7. Lateral positions in situs inversus without ventricular inversion or in situs solitus with ventricular inversion. Diagrams representing the different truncoconal morphologies as a sign for the identification of the spatial position of the ventricular chambers. In the case of crossed arteries, the direction from left to right of the pulmonary artery (*PA*) indicates that the anatomically right ventricle (*RV*) is placed on the left; in the case of transposed arteries the left sided position of the aorta (*Ao*) with respect to the pulmonary artery indicates the left sided position of the anatomically right ventricle. The left-to-right direction of the common trunk (*CT*) indicates that the anatomically right ventricle is placed on the left side. *LV* = anatomically left ventricle. *TGV* = transposition of the great vessels.

group of truncoconal morphologies are not the object of this study because of their peculiar anatomic and embryologic features which do not conform to the rules given for the localization of the ventricles.

Diagnosis of the size of the cardiac chambers

The inspection of the atria is important in order to ascertain their size—either normal, small or enlarged. For instance, right atrial enlargement along with other signs is a very valuable sign in the diagnosis of atrial septal defects, while a small left atrium associated with other cardiac anatomic signs is an indirect sign of a total anomalous pulmonary venous connection.

In the examination of the ventricles it is important to determine if they are normal, enlarged or small. In order to define their dimensions one must previously establish the external limits of each one of them by *means* of the path of the coronary arteries—the anterior descending and the posterior descending—which indicate indirectly the position of the ventricular septum, of the atrioventricular grooves which point the atrioventricular valvular level, and also to determine the borders of the heart at the ventricular level. There is an indirect sign which permits one to *suspect if the ana*tomically right ventricle is enlarged due to hypertrophy or to dilatation. This information is supplied by the aspect of the external border of this ventricle: if it is sharp it indicates hypertrophy and if it is blunt it depicts dilatation. This sign is not useful or applicable to the study of *hypertrophy* or dilatation of the anatomically left ventricle because of the ventricle's normal conic shape.

A small anatomically left ventricle is a sign of most importance in the diagnosis of congenital mitral stenosis along with the study of other cardiac signs.

The presence of the anterior and posterior descending coronary arteries represented by two small branches similar to other numerous vertical branches which arise from the coronary arteries in their course along the atrio*ventricular* grooves strongly suggests the diagnosis of a single ventricle, but the absence of this sign does not exclude such a diagnosis.

Summary

A series of rules for the diagnosis of visceral situs, truncoconal morphologies, spatial position of the ventricles and atrioventricular relations are presented. These rules are based on anatomoembryologic concepts and therefore they are applicable to the radiologic and angiocardiographic study of congenital cardiopathies.

1. A situs solitus is characterized because of the presence of an anatomically right atrium placed on the right, which is identified radiologically by the right sided position of the suprahepatic portion of the inferior vena cava. Situs inversus is characterized by an anatomically right atrium placed on the left, which is identified radiologically by the left position of the suprahepatic portion of the inferior vena cava.

2. In order to diagnose truncoconal morphologies it is necessary to specify first the presence of one or two arteries arising from the heart. If a single artery arises from the heart it is a common trunk. When two arteries arise from the heart there are two main truncoconal morphologies: (a) the arteries cross each other in space—the pulmonary artery crosses obliquely in front of the aorta; and (b) transposition of the great arteries—the aorta is then anterior and parallel to the pulmonary artery.

3. By means of the truncoconal morphologies the spatial position of the ventricles is identified. When the arteries cross each other (without transposition) the right to left direction of the pulmonary *artery indicates that the anatomically right* ventricle is placed on the right side and vice versa. When the great arteries are transposed, the right-sided position of the aorta with respect to the pulmonary artery indicates that the anatomically right ventricle is on the right side and vice versa. The direction of the common trunk from right to left indicates the right sided position of the anatomically right ventricle and vice versa. This rule is also valid for lateral positions of the great arteries (dextro and levopositions).

4. Once the visceral situs is diagnosed by means of the position of the suprahepatic segment of the inferior vena cava and the spatial position of the ventricles

with the type of situs of which they form part Thus a d transposition in a situs solitus causes the anatomically right atrium to connect with the aorta through an anatomically right ventricle placed on the right and gives rise to the clinical picture of transposition of the great arteries (Figs 1*E* and 4*A*) The d transposition in situs inversus on the other hand, causes the anatomically *left* atrium to communicate with the aorta through an anatomically right ventricle placed on the right without *any hemodynamic consequence* if there are no added malformations, since it is a ventricular inversion with transposition of the great arteries also *designated as "corrected* transposition of the great arteries" although this latter designation seems to us incorrect (Figs 2*H* and 4*D*)

3 *Common trunk* In common trunk the important feature is the direction of the single vessel in space If it is directed from the right to the left the anatomically right ventricle is placed on the right side (Figs 1*F* 2*I* and 5*A*) If it is directed from left to right the anatomically right ventricle is placed on the left side (Figs 1*I* 2*F* and 5*B*) The hemodynamic and angiocardiographic diagnosis *is made with a frontal* x ray film

Regardless of the absence of a truncoconal septum (*common trunk*) or of a straight septum (transpositions) or of a rotated septum (great arteries which cross each other in space), the truncus conus in the embryo connects with the anatomically right ventricle and later becomes displaced toward the midline in order to become biventricular which is the normal position (orthoposition)[17] If the truncus conus remains in the embryonic position a dex*troposition* takes *place* in which both vessels or the common trunk arise from the anatomically right ventricle or a vessel arises from this ventricle and the other one overrides the ventricular septum (dextropositions) (Fig 6A_1 A_2 and A_3 and Fig 7A_1 A_2 and A_3) If there is an abnormal displacement and *the truncus conus* remains connected with the anatomically left ventricle both vessels or the common trunk arise *from* this ventricle or one of them overrides the septum and the other one arises from the anatomically left ventricle (levopositions)[10] (Fig 6 C_1 C_2 and C_3 and Fig 7C_1 C_2 and C_3)

The rules for orthoposition are valid fo the location of the ventricles through th truncoconal morphologies both in levo positions and in dextropositions For in stance in the case of arteries which cros each other in space the right to left direc tion of the pulmonary artery indicates tha the anatomically right ventricle is placed o the right side, even though (1) the grea arteries arise from this ventricle or (2) bot of them arise from the anatomically le ventricle or (3) else one of them overrid the septum and the other one arises fro *the anatomocally right or left* ventricl (Fig 6 A_1, B_1, and C_1)

In general, in levopositions the anator cally *right* ventricle is *hypoplastic* in spit of which the rules previously mentione apply, since in these cases the ventricl that is properly developed has the anatomi features of the left ventricle

In transposition of the great arteries th aorta placed on the left of the pulmonar artery indicates that the anatomically righ ventricle is placed on the left side regard less of whether both arteries arise fro this ventricle both from the anatomicall left ventricle, or one of them overrides the septum and the other arises from the an atomically right or left ventricle (Fig 7A_2 B_2 and C_2)

After having located the ventricles spatially by means of the study of the truncoconal morphologies the relation of the ventricles with their atria is established —that is with the visceroatrial situs of which they are part (anatomically right atrium suprahepatic portion of the inferior vena cava greater lobe of the liver) For *instance*, if the anatomically right ventricle is placed on the left and connects with the atrium which receives the suprahepatic portion of the inferior vena cava and the greater lobe of the liver is placed on the left the diagnosis of normally placed ventricles in situs inversus is made (Fig 2*B* and 3*C*) *however if it connects with an* atrium which does not have that vein and the greater lobe of the liver is on the right it is a ventricular inversion in situs solitus (Figs 1*C* and 3*B*)

Partial distortions although merely a

Pulmonary cineangiography in acute pulmonary embolism

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Pulmonary angiography is widely accepted as the most definitive technique available for the diagnosis of acute pulmonary embolism.[1] The angiographic abnormalities that are diagnostic of acute pulmonary embolism are intraluminal filling defects and/or arterial cutoffs.[2,3] However, in our experience the primary limitation of this technique is that some angiographic studies are equivocal because it is not possible to be certain of the presence of these two diagnostic abnormalities. In a series of 247 consecutive patients with suspected pulmonary embolism studied by conventional cut film pulmonary angiography, we noted equivocal results in 17 per cent.[3]

This study was undertaken to determine if selective pulmonary cineangiography—used as an adjunct to conventional pulmonary angiography—could be useful in establishing a definitive diagnosis in equivocal cases.

Materials and methods

Patient selection. Pulmonary cineangiography was performed in 14 patients whose conventional cut film angiographic studies were equivocal for acute pulmonary embolism. Cineangiography was also performed in 22 additional patients whose conventional angiographic study had been definitive—i.e., positive for pulmonary embolism in 16 and negative in 6. The total incidence of equivocal results by conventional pulmonary angiography during the time of this study was 16 per cent.

Angiographic techniques. Conventional pulmonary angiography was performed by previously described techniques.[3] Sixty ml. of contrast medium was injected into the main pulmonary artery or right ventricular outflow tract at an injection rate of 25 to 30 ml. per second. Twelve films were taken at a rate appropriate to visualize arterial, capillary, and venous phases. When indicated, repeat cut film angiograms with selective injection into areas in question were performed with oblique projections.

Pulmonary cineangiograms were performed by injecting 20 to 30 ml. of contrast medium into the main right or left pulmonary arteries or their first order subdivisions at 15 to 20 ml. per second, utilizing a closed

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is ascertained by means of the truncoconal morphologies one proceeds to establish the *atrioventricular relations which number* two for each situs—normal atrioventricular relation (*atrioventricular concordance*) or ventricular inversion (atrioventricular discordance)

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tip angiographic catheter. Filming was at 64 frames per second using an Arriflex camera and a six inch image intensifier. Shutters were positioned to exclude high density anatomic structures such as adjacent heart border, spine, or diaphragm. Choice of positioning was dependent on the anatomy of the particular area to be visualized as determined by analysis of the conventional angiograms.

Interpretation of angiographic and cineangiographic results

Conventional angiograms were read by four to six of the investigators at the time of the study. Cineangiograms were interpreted by the same investigators when they were developed two to four hours later, with knowledge of the results of the conventional angiograms. Independent and/or individual evaluation of the two techniques was judged to be incompatible with optimal patient care and unnecessary in view of the intended use of cineangiography as a supplement to conventional angiography.

The diagnosis based upon each technique was then determined as being definitely positive, definitely negative, or equivocal. Studies upon which agreement could not be reached by all investigators were listed as equivocal, even though individual investigators considered them definitely positive or negative.

Results

Of the 16 patients in whom the results of conventional angiography were considered definitely positive, the use of cineangiography led to a change of diagnosis in only one (Table I). In this case (Table II, Case 1) the conventional angiogram was thought to show an intraluminal filling defect in the main artery to the left lower lobe. Cineangiography revealed entirely normal filling of the artery in question. However, as contrast medium was washed out of the large artery, more distally located smaller vessels still contained contrast medium and overlapped the larger vessel in such a manner as to simulate the appearance of a filling defect. In the other 15 patients whose conventional angiograms were positive, the cineangiogram showed abnormalities in the same arteries that had been abnormal by conventional angiography.

Of the six conventional angiographic studies considered definitely negative, no diagnosis was changed by the results of the cineangiographic studies (Table I). However, of the 14 conventional angiographic studies that had been equivocal, the use of supplementary pulmonary cineangiography led to a definitive diagnosis in 13. In eight of these cases, the cineangiographic studies demonstrated no evidence of pulmonary embolism in the areas in question. In each instance a satisfactory explanation for the equivocal angiographic appearance was apparent. These mechanisms are detailed for the individual cases in Table II. In five other equivocal cases, cineangiographic studies delineated definite intraluminal filling defects or arterial cutoff in the questionable areas. Thus the final diagnoses were changed to definite pulmonary embolism in these five cases. The cineangiographic findings which permitted a definitive diagnosis are listed for the individual cases in Table II. In one case the results were considered equivocal by both techniques.

Confirmation of angiographic and cineangiographic results

Postmortem confirmation of the combined angiographic and cineangiographic studies was obtained in two patients. One patient died six weeks after a study in which an equivocal angiographic diagnosis was changed to definitely positive by the cineangiographic study. In the interim she had received thrombolytic therapy followed by continuous anticoagulation. At autopsy the large vessels were clear, but large numbers of organizing thromboemboli were found in the smaller pulmonary arteries. The cause of death was unrelated to pulmonary embolism. A second patient died two weeks after a study that was positive by both techniques. Autopsy revealed massive pulmonary embolism, both old and new, arising from a mural thrombus on the right side of his infarcted ventricular septum.

Discussion

The angiographic abnormalities that are diagnostic of pulmonary embolism, namely filling defects and arterial cutoffs, are under some circumstances difficult to recognize

Table I. Influence of cineangiographic study on angiographic diagnosis

Angiographic diagnosis	Number	Final diagnosis—(angiogram and cineangiography)		
		Definite	*Equivocal*	*Negative*
Definite	16	15	0	1
Equivocal	14	5	1	8
Negative	6	0	0	6
	36			

Table II. Cases in which final diagnosis was changed on basis of pulmonary cineangiography

Case	Conventional angiography*		Cineangiography	
	Findings	*Diagnosis*	*Findings*	*Diagnosis*
1	Definite Filling Defect RLL	Definite	Overlapping structures—No FD	Negative
2	Filling Defect RLL (?) Cutoff LLL (?)	Equivocal	Overlapping structure—no FD and no CO	Negative
4	Cutoff RLL (?)	Equivocal	Stationary FD seen being enveloped by contrast medium	Definite
5	Filling Defect, RUL (?)	Equivocal	Small clot seen in motion	Definite
9	Linear Filling Defect LUL (?)	Equivocal	Parallel artery and vein opacify sequentially—no FD	Negative
15	Filling Defect and Cutoff LUL (?)	Equivocal	Long coiled clot seen in motion—one end impacted in LUL branch	Definite
16	Filling Defects RLL LLL (?)	Equivocal	Overlapping structures—no FD	Negative
17	Cutoff RLL (?)	Equivocal	Definite CO among several overlapping vessels in atelectatic segment	Definite
25	FD LLL (?)	Equivocal	Overlapping structures no FD	Negative
26	FDs RLL LLL (?)	Equivocal	Overlapping structures—no FD	Negative
28	FD RLL (?)	Equivocal	Stationary FD seen being enveloped by contrast medium	Definite
29	FD RLL (?)	Equivocal	Overlapping structures no FD	Negative
32	FD and CO RUL (?)	Equivocal	Continuity of flow through vessels distorted by bullae	Negative
35	FD RLL (?)	Equivocal	Overlapping structures no FD	Negative

*Abbreviations: FD = filling defect CO = cutoff RLL = right lower lobe LLL = left lower lobe LUL = left upper lobe RUL = right upper lobe

or distinguish from other normal or abnormal anatomic structures in the lung. The value of supplemental pulmonary cineangiography in this setting derives from its capacity to delineate motion and flow characteristics.

For example, intraluminal clots when they are incompletely obstructing may be obscured by contrast medium passing around them[4,5] and can occasionally be overlooked or be difficult to recognize on conventional angiograms. Cineangiography may permit visualization of such incomplete obstructions by revealing the complete sequence of movement of the contrast medium as it flows around and envelops the clot. Also if portions of the clot are pedunculated they may readily be seen moving during the rapid systolic flow. This is a striking finding when present and pro

vided the basis for changing the diagnosis to positive in two patients whose conventional angiograms were considered to have been equivocal. It was also observed in several patients whose conventional angiograms had been positive.

The ability to perceive the details of sequential flow may be helpful in other situations. In one instance an artery was parallel to an adjacent pulmonary vein. When both were opacified the resultant radiolucent space between them closely resembled a linear filling defect within a single vessel on the conventional angiogram. The cineangiogram readily clarified the anatomy by demonstrating that the artery filled much earlier than the vein and from the opposite direction.

In our experience the commonest cause of difficulty in interpreting conventional angiograms is the presence of overlapping structures, which by addition or subtraction of radiodensity at critical points may simulate filling defects or cutoffs. Repeat angiograms in oblique projections are often helpful by changing the alignment of the overlapping structures. At times, however, this approach succeeds only in substituting another confusing array of overlapping structures. We have found cineangiography to be especially useful in this situation because of its ability to demonstrate relative motion between overlapping structures. This often allows differentiation of vessels from one another, from overlying bronchi, or from portions of the cardiac shadow.

Similarly, the ability to appreciate sequential filling and relative motion may be extremely helpful in distinguishing a true arterial cutoff from an artery that simulates this appearance by bifurcating into two end-on branches. Here, cineangiographic visualization of slight moment to moment changes in orientation of the end-on branches, as well as sequential appearance of their more distal branches, often permits an accurate assessment of the anatomy.

Other techniques for enhancing the diagnostic accuracy of pulmonary angiography have been devised. In particular, magnification angiography[6] and multisection angiography[4] have been reported to be useful in this regard.

We have not had the opportunity to compare pulmonary cineangiography t either of these techniques. Cineangiograph does, however, have one advantage relati to either of them in that it is readily avai able in nearly all laboratories that perfor cardiac catheterization and related pro cedures.

A disadvantage of pulmonary cineangiog raphy is the relatively longer time require for film development. Our preliminary ex perience with using a video tape record for instant playback of the cine results ha been quite favorable in spite of the inheren small loss of resolution.

No complications were encountered wit the use of cineangiography. In general there was less flushing, nausea, and cough ing with the cineangiographic studies tha with conventional angiography. This wa probably due to the fact that smalle amounts of contrast medium were injecte for the cineangiographic studies.

Conclusions

Selective pulmonary cineangiography wa found to be a safe and useful adjunct t conventional pulmonary angiography. It ability to show relative motion betwee overlapping structures and the details o flow within the pulmonary arteries can b very useful in arriving at a definitive diag nosis when the results of conventiona angiography are equivocal.

Summary

The usefulness of selective pulmonar cineangiography as a supplement to con ventional pulmonary angiography was eval uated in 36 patients. In 13 of the 14 patient whose conventional angiographic result were equivocal, pulmonary cineangiogra phy of questionable areas permitted definitive diagnosis to be made. In 21 of th 22 patients whose conventional angio graphic studies were considered definitel positive or negative, the cineangiographi results were in complete agreement. Thus the principal value of supplemental pulmo nary cineangiography is in patients whos conventional angiograms yield equivoca results. Its usefulness in this situatio derives from its ability to delineate th details of flow and motion within the pul monary vasculature.

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We have not had the opportunity to compare pulmonary cineangiography to either of these techniques. Cineangiography does, however, have one advantage relative to either of them in that it is readily available in nearly all laboratories that perform cardiac catheterization and related procedures.

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Summary

The usefulness of selective pulmonary cineangiography as a supplement to conventional pulmonary angiography was evaluated in 36 patients. In 13 of the 14 patients whose conventional angiographic results were equivocal, pulmonary cineangiography of questionable areas permitted a definitive diagnosis to be made. In 21 of the 22 patients whose conventional angiographic studies were considered definitely positive or negative, the cineangiographic results were in complete agreement. Thus, the principal value of supplemental pulmonary cineangiography is in patients whose conventional angiograms yield equivocal results. Its usefulness in this situation derives from its ability to delineate the details of flow and motion within the pulmonary vasculature.

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Incomplete bilateral bundle branch block and A-V block complicating acute anterior wall myocardial infarction

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In recent years physicians have become aware of the high mortality rate of complete heart block (CHB) associated with acute anterior wall myocardial infarction (MI). Norris[1] noted a 5 per cent incidence of CHB with acute anterior wall MI and a 75 per cent mortality rate in this group. Lassers and Julian[2] noted that 10 of their 11 patients with anterior wall MI who developed CHB died. Similar findings were also reported by Friedberg and associates.[3]

Since the mortality rate of this condition is high, attention has been focused on recognizing electrocardiographic (ECG) patterns which will help in predicting the onset of CHB or asystole. Godman and associates[4] stress the importance of a bilateral bundle branch block pattern preceding the appearance of CHB. These investigators reported that 71 per cent of a group of patients with acute MI developed CHB shortly after a pattern of bilateral bundle branch block was recognized. The mortality rate in this group was extremely high (18 of 21 died).

During a five year period (1965-1970) 30 patients with acute anterior wall myocardial infarction complicated by CHB or a form of incomplete bilateral bundle branch block (IBBBB) were managed in a coronary care unit. The purpose of this report is to review our experience with this group with particular reference to ECG and clinical features of prognostic importance and to evaluate the role of artificial pacing in management.

Methods

Definitions. Confirmation of acute MI required abnormal Q waves and serial ST-T changes as well as characteristic serum creatinine phosphokinase and transaminase abnormalities. The classification used for anterior wall infarction included the criteria of Meyers and associates[5,6] for anteroseptal and anterolateral MI.

Right bundle branch block (RBBB) and left bundle branch block (LBBB) were defined according to the criteria of the New York Heart Association and included a QRS duration of 0.12 second or more.[7] Patients with RBBB and a Q wave in V_1 were not listed separately.

The following criteria were employed for the diagnosis of incomplete bilateral bundle branch block (IBBBB) variant as observed

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among our patients RBBB with left anterior hemiblock (LAHB) RBBB with left posterior hemiblock (LPHB) alternating LBBB and RBBB in the same or in serial tracings first-degree A V with bundle branch block and unusually prolonged QRS[8] and Mobitz type II A V block

Mobitz type II A V block is defined as failure of a ventricular response without antecedent progressive lengthening of the A V conduction time[9] This type of A V block has been classified as one of the ECG manifestations of bilateral bundle branch block[8] It is recognized that exceptions exist[10] but this would require His bundle recording for documentation

Patients and procedures There were 18 men (average age 66 range 39 to 80) and 12 women (average age 74 range 59 to 86) A history of antecedent heart disease could be obtained in only ten patients Any patient with previous ECG evidence of IBBBB was excluded from the study

The patients were followed in a coronary care unit with oscilloscopic monitoring at each bedside All patients had a standard 12 lead ECG daily and more frequently if any evidence of A V or I V conduction defect was noted on the oscilloscope Ventricular fibrillation or ventricular standstill were observed on the oscilloscope and in some cases were graphically recorded Deaths due to terminal cardiogenic shock or congestive heart failure were not listed as arrhythmia deaths During the first three years of this study temporary transvenous pacing electrodes were inserted only after the appearance of CHB or ventricular standstill Over the last two years the indication for temporary pacing was expanded to include all patients with RBBB and IBBB patterns

None of the patients was lost to follow up The follow up period of surviving patients ranges from three years to seven months Postmortem information is available on four patients.

Results

Of the total group of 30 patients 19 (63 per cent) died during their initial hospitalization The initial hospitalization period was four weeks There were two deaths in the fourth week but the majority occurred in the first week There was one late sudden death at eight months with cause undetermined

Seven patients had no evidence of either A V or complete bundle branch block on admission (Table I) Two of these seven patients had LAHB on admission Five patients developed CHB between the first and seventh day In all cases CHB was preceded by some degree of intraventricular block by a period of several hours to two days Of the two patients in this group who did not develop CHB one developed RBBB and LAHB on day 3 The RBBB disappeared on day 4 but the patient died in shock and congestive heart failure on day 10 The other patient who did not develop CHB had evidence of both inferior and anterior wall myocardial infarction and developed Mobitz type I A V block on day 3 and Mobitz type II A V block on day 4 He is alive at four months

Fourteen patients presented with evidence of IBBBB on admission (Table II) Within this group ten patients developed CHB or ventricular standstill within the first seven days Six of the latter died Two patients died in ventricular standstill before pacing could be initiated One patient died suddenly (unmonitored) on day 23 one week after the pacemaker had been removed The remaining three patients died in cardiogenic shock Four patients continued with the pattern they had on admission One with LAHB and RBBB is alive at four months the other with first degree A V block LPHB and RBBB died in ventricular fibrillation on day 5 CHB occurred late in two patients one on day 25 and another at 18 months

Of four patients with RBBB on admission (Table III) one developed CHB (day 1) and two ventricular standstill (day 1 day 7) All three died—one in cardiogenic shock one in CHB and one in ventricular standstill The latter two patients died before pacing could be initiated The fourth patient in this group developed IBBBB (RBBB and LAHB) on day 3 and is alive at six months with this ECG pattern

All three patients who had LBBB on admission (Table IV) died after developing CHB—two in shock and one in ventricular standstill

Two patients had CHB on admission (Table V) One is alive at 14 months with a

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Table II Patients with ECG evidence of IBBB on admission

No	Age	Sex	ECG on admission	AV or IV block	Pacemaker	Complications	Final disposition
8 T C	0	M	NSR Mobitz type I AV RBBB (QRS 0 15 sec)	CHB then ventricular standstill 5 hr			Died ventricular standstill 5 hr
9 S T	65	M	NSR LAHB RBBB	CHB (rate 60) day 7	Inserted day	Shock	Died day shock
10 J M	64	F	NSR Mobitz type I AV LAHB RBBB	Ventricular standstill day 4	Inserted day 4	Shock day 8	Died, shock day 8
11 D P	5	M	NSR LAHB RBBB	Same	Inserted day 1 removed day 14	Mild CHF	Alive NSR LAHB RBBB 4 mo
12 E V	9	F	NSR LAHB RBBB	Mobitz type II AV day 4 CHB (rate 45) day 5	Inserted day 1 removed day 0		Discharged day CHB asymptomatic (patient) refused pacemaker
13 G H	5	M	NSR LAHB RBBB	Ventricular standstill day 1 LAHB day 2	Inserted day 1 removed day 14		Alive LAHB yr
14 F G	80	F	NSR LAHB RBBB	Ventricular standstill day ?	Inserted day	Intermittent SA block day 1	Died ventricular standstill day before pacing could be initiated
15 F P	73	F	NSR LAHB RBBB	NSR LBBB day 1 Mobitz type II AV day 1 ventricular standstill day 1 atrial fibrillation LBBB day 3 NSR Mobitz type I AV with LBBB day 4	Inserted day 1 removed day 1	Mild CHF	Alive NSR Mobitz type I AV LBBB 13 mo
16 H M	30	F	NSR Mobitz type II AV RBBB	CHB day	Inserted day 1 permanent (demand) pacemaker 1 mo	Moderate CHF intermittent ventricular tachycardia	Died, 8 mo sudden cause unknown
17 H S		M	NSR Mobitz type I AV LAHB RBBB	NSR, Mobitz type I AV LPHB RBBB day 5	Inserted day 1		Died, ventricular fibrillation day 5
18 A L	61	F	NSR Mobitz type II AV LPHB RBBB	CHB 1 hr (rate 45)	Inserted 1 hr	Progressive CHF and shock	Died, day 3 shock
19 P C		M	NSR, LAHB RBBB	Mobitz type II AV day 1 CHB (rate) 28) day 1 NSR LAHB RBBB day 4	Inserted day 1 removed day 1	Mod. CHF	Alive NSR LAHB RBBB 16 mo
20 F V	80	M	NSR Mobitz type II AV LAHB RBBB	NSR LAHB RBBB day CHB 18 m	Inserted day ? removed day 3 permanent demand 18 mo		Alive 3 yr demand pacemaker
1 C E	6	M	Atrial fibrillation LAHB RBBB	NSR LAHB RBBB day ventricular standstill day 6		CHF	Died day 6 ventricular standstill

Table I. Patients with no evidence of A V or IBBB on admission

No	Age	Sex	ECG on admission	A V or I V block	Pacemaker	Complications	Final disposition
1 M B	56	M	Sinus tachycardia	Mobitz type II A V and LBBB day 2 CHB day 3 and ventricular standstill	Day 3 with CHB removed day 15		NSR with LAHB day 6 pacemaker removed day 15 died ventricular standstill day 23
2 K V	69	F	Sinus tachycardia	Mobitz type II A V LAHB and RBBB day 3 CHB day 3	Inserted day 3 with CHB	Pulmonary edema and shock day 3	Died shock day 3
3 G D	69	F	NSR (normal sinus rhythm)	Atrial flutter RBBB day [illegible] CHB day 7 NSR with LAHB day 9 ventricular standstill day 11	Inserted day 7 with CHB paced again day 11	Shock day 25	Died day 25 shock
4 M V	[illegible]	M	NSR	Mobitz type II A V day 2 CHB (rate 28) day 2	Inserted day [illegible]	Shock	Died day [illegible] shock
5 I H	86	F	NSR LAHB	Intermittent CHB (rate 50) day 1 NSR with LAHB day 2 NSR day 8	Inserted day 1 removed day 14	Pulmonary edema persistent CHF frequent VPS	Alive 14 mo NSR
6 H O S	60	M	NSR LAHB	RBBB with LAHB day 3 LAHB day 4	Inserted day 3	Shock CHF	Died shock and CHF day 10
7 G H	60	M	NSR combined inferior and anterior MI	Mobitz type I A V day 3 Mobitz type II A V day 4	Inserted day 4	CHF	Alive 4 mo NSR

permanent demand pacemaker The other died in shock on day 10

Thus 21 of these 30 patients exhibited IBBBB Ten progressed to CHB six developed ventricular standstill and five showed either no progression or regression of IBBBB The mortality rate in this group was 62 per cent

Ten patients of all 21 with bilateral bundle branch block were observed to have periods of Mobitz type II A V block Seven patients developed CHB one ventricular standstill, and two returned to normal A V conduction during their initial hospitalization One of these latter two patients developed CHB 18 months later

Mobitz type II A V block was observed in association with RBBB in six patients and with LBBB in two patients Its duration was usually a matter of minutes but periods lasting three six and eight hours were seen

Of the entire group CHB and ventricular standstill occurred in 21 patients (70 per cent) during the first seven days Of the 21 patients who developed CHB or ventricular standstill during the first seven days 16 died—nine in shock and the remaining seven of their arrhythmia

Recurrent ventricular standstill was observed in four patients who had normal A V conduction but who had previously exhibited CHB In all four patients intraventricular conduction disturbances (LBBB, LAHB + RBBB LPHB + RBBB, and LAHB) were noted prior to the recurrent asystole

Twenty six patients had pacemaker insertion—13 because of sudden onset of CHB Seven died in shock and three in ventricular standstill There was one late death at 23 days (unmonitored) after the temporary pacemaker had been removed Two patients are alive at 14 and 16 months Four patients had pacemaker insertion because of sudden ventricular standstill Two died in shock one continued in ventricular standstill and could not be paced one is

Table II. Patients with ECG evidence of BBB on admission

No	Age	Sex	ECG on admission	A-V or I-V block	Pacemaker	Complications	Final disposition
8 T C	[illegible]0	M	NSR Mobitz type I A-V RBBB (QRS 0.15 sec)	CHB then ventricular standstill 5 hr			Died ventricular standstill 5 hr
9 S T	6[illegible]	M	NSR LAHB RBBB	CHB (rate 60) day [illegible]	Inserted day	Shock	Died day 7 shock
10 J M	64	F	NSR Mobitz type I A-V LAHB RBBB	Ventricular standstill day 4	Inserted day 4	Shock day 8	Died shock day 8
11 D R	5[illegible]	M	NSR LAHB RBBB	Same	Inserted day 1 removed day 14	Mild CHF	Alive NSR LAHB RBBB 4 mo
12 F A	[illegible]9	F	NSR LAHB RBBB	Mobitz type II A-V day 4 CHB (rate 48) day 5	Inserted day 1 removed day 20		Discharged day [illegible] CHB asymptomatic (patient) refused pacemaker
13 G H	[illegible]5	M	NSR LAHB RBBB	Ventricular standstill day 1 LAHB day 2	Inserted day 1 removed day 14		Alive LAHB [illegible] yr
14 F G	80	F	NSR LAHB RBBB	Ventricular standstill day	Inserted day 2	Intermittent SA block day 1	Died ventricular standstill day 2 before pacing could be initiated
15 F P	73	F	NSR LAHB RBBB	NSR LBBB day 1 Mobitz type II A-V day 1 ventricular standstill day 1 atrial fibrillation LBBB day 3 NSR Mobitz type I A-V with LBBB day 4	Inserted day 1 removed day 21	Mild CHF	Alive NSR Mobitz type I A-V LBBB 13 mo
16 H M	[illegible]0	F	NSR Mobitz type II A-V RBBB	CHB day [illegible]	Inserted day 1 permanent (demand) pacemaker 1 mo	Moderate CHF intermittent ventricular tachycardia	Died 8 mo sudden cause unknown
17 H S	[illegible]	M	NSR Mobitz type I A-V LAHB RBBB	NSR Mobitz type I A-V LPHB LBBB day 5	Inserted day 1		Died ventricular fibrillation day [illegible]
18 A P	61	F	NSR Mobitz type II A-V LPHB RBBB	CHB 1 hr (rate 45)	Inserted 1 hr	Progressive CHF and shock	Died day 3 shock
19 P C	[illegible]	M	NSR LAHB RBBB	Mobitz type II A-V day 1 CHB (rate 28) day 1 NSR LAHB RBBB day 4	Inserted day 1 removed day 1	Mod. CHF	Alive NSR LAHB RBBB 16 mo
20 F A	60	M	NSR Mobitz type II A-V LAHB RBBB	NSR LAHB RBBB day [illegible] CHB 18 m	Inserted day 2 removed day 3 permanent demand 18 mo		Alive 3 yr demand pacemaker
21 C F	6[illegible]	M	Atrial fibrillation LAHB RBBB	NSR LAHB RBBB day [illegible] ventricular standstill day 6		CHF	Died day 6 ventricular standstill

Table III Patients presenting with RBBB on admission

No	Age	Sex	ECG on admission	A V or I V block	Pacemaker	Complications	Final disposition
22 C F	78	M	Sinus tachycardia RBBB	CHB (rate 70) day 1		Pulmonary edema	Died CHB day 1
23 M M	76	M	NSR RBBB	CHB ventricular standstill day 1	Inserted day 1	Shock	Died day 1 shock
24 K F	63	M	Sinus tachycardia RBBB	Ventricular standstill day 7		Shock	Died ventricular standstill day 7
25 J M	39	M	Sinus tachycardia RBBB	NSR LAHB RBBB day 3	Inserted day 3 removed day 14	Mild CHF frequent VPs	Alive 6 mo NSR LAHB RBBB

Table IV Patients with LBBB on admission

No	Age	Sex	ECG on admission	A V or I V block	Pacemaker	Complications	Final disposition
26 M S	76	F	Sinus tachycardia LBBB	CHB (rate 70) day 2 ventricular standstill day 3	Inserted day 2	Mild CHF	Died ventricular standstill day 3 pacemaker failed to function
27 H N	47	F	NSR LBBB	CHB day 2 (rate 60)	Inserted day 2		Died day 2 shock
28 S L	67	M	NSR LBBB	CHB day 1 (rate 30)	Inserted day 1	Shock	Died shock day 1

alive at 13 months Nine patients had pacemaker insertion as a prophylactic measure because of recognition of RBBB or one of the patterns of IBBBB Three of these patients died—one in shock, one in ventricular fibrillation, and one at 8 months with a functioning permanent pacemaker (arrhythmia is a likely cause of death) Two patients progressed to either CHB or ventricular standstill within the first hospital week and are still alive at 4 months and 24 months The four patients who did not develop CHB or ventricular standstill during their initial hospitalization are alive at 4, 4 6 and 18 months

Complications encountered during pacemaker insertion included multiple ventricular premature systoles and episodes of ventricular tachycardia These were all promptly treated and were not thought to influence the patient s subsequent course

Postmortem examinations revealed extensive acute anteroseptal infarction In one patient old posterior wall infarction was also noted Detailed studies of the conduction pathways were not performed

Discussion

In our group of patients 76 per cent of those who showed a pattern of IBBBB progressed to either CHB or ventricular standstill This high incidence has been noted by others[4 11 1] The most common manifestation of IBBB leading to these complications has been RBBB + LAHB[11 12] Mobitz type II A V block has been noted occasionally to be a precursor of CHB in acute anterior wall myocardial infarction[13]

Ten of our patients (33 per cent) had periods of Mobitz type II A B block Seven of these patients developed CHB or ventricular standstill within the first week One developed complete heart block on day 25 and another at 18 months Thus, a total of 90 per cent of these patients required a pacemaker following the recognition of Mobitz type II A V block

The question of prophylactic pacemaker

Table V Patients with CHB on admission

No	Age	Sex	ECG on admission	A V or I V block	Pacemaker	Complications	Final disposition
29 V T	80	M	NSI CHB (rate 70)		Inserted day 1 permanent demand pacemaker inserted 1 mo	Mild CHF	Alive permanent demand pacemaker 14 mo
30 J K	9	F	NSR CHB (rate 0)	NSR LAHB RBBB day ventricular standstill day 3	Inserted day 1 pacemaker responded	CHF shock	Died day 10 shock

insertion once these patterns are recognized remains unsettled Godman and colleagues [4] who recognized the high mortality rate of bilateral bundle branch block concluded that the serious risk of electrode insertion was not warranted because of the small potential gain Roos and Dunning[11] describe prophylactic pacemaker insertion in ten patients with IBBBB pattern Although CHB and ventricular standstill were treated the death rate remained high because of cardiogenic shock Scanlon and co workers[12] observed a slightly better prognosis They felt that insertion of a prophylactic pacemaker was indicated because it did improve prognosis

Temporary pacemakers were inserted in 86 per cent of our patients (26 patients) The mortality rate of this group was 61 per cent The major factor contributing to death was the severity of myocardial infarction as manifested by the high incidence of cardiogenic shock and refractory congestive heart failure This experience has been noted by others [4, 11] Pacemaker therapy was thought to contribute to the management of patients less severely ill by facilitating the management of heart failure and superimposed serious ventricular arrhythmias and by preventing recurrent ventricular standstill

There were four patients who did not have pacemakers inserted because IBBBB patterns were not recognized all four died in CHB or ventricular standstill One may speculate as to the probable benefit of pacing since their course was not complicated by shock or congestive heart failure

One of the questions raised by this study is when to remove a temporary pacemaker catheter Patient No 1 died suddenly and unexpectedly on day 23 This patient presented with IBBB and progressed to CHB His temporary pacemaker was removed nine days after IBBB disappeared Although this represented only one example of sudden and unexpected death in a group of three with IBBB and transient CHB the larger experience of Atkins and associates[14] would suggest a more significant mortality rate Further studies are clearly indicated to determine the need for permanent pacemaker implantation

It is concluded from this study that insertion of a temporary electrode catheter is warranted in all patients with acute anterior wall myocardial infarction who show evidence of IBBBB Although the length of time the pacemaker should remain in place is not clear it is our practice to maintain this catheter in position for 21 days unless this is prohibited by complications produced by the catheter

It is hoped that more sophisticated studies utilizing His bundle recording will assist in determining the time of temporary catheter removal and necessity of permanent pacemaker implantation

Summary

Thirty patients with incomplete bilateral bundle branch block (IBBBB) or atrio ventricular (A V) block complicating acute anterior wall myocardial infarction are discussed The hospital mortality rate of this group was 63 per cent Of patients who developed IBBBB 76 per cent progressed to either complete heart block ventricular standstill or ventricular fibrillation Findings that are stressed are the high incidence

of Mobitz type II A V block and recurrence of life threatening arrhythmias It is concluded that a temporary electrode catheter is warranted in this group of patients

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Left anterior hemiblock and right bundle branch block before and after surgical repair of tetralogy of Fallot

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Recently the occurrence of left anterior hemiblock and right bundle branch block (RBBB) has been reported following total surgical correction of tetralogy of Fallot.[1-4] This complication is related to surgical damage of the anterior branch of the left bundle as well as to damage of the right bundle of the conducting system which are in close relationship to the posterior margin of the ventricular septal defect.[5, 6] In the presence of RBBB when the mid vector points to the left at $-30°$ or more, the postoperative electrocardiogram (ECG) resembles that of endocardial cushion defect. It is of interest that RBBB and the combination of left anterior hemiblock (LAH) and RBBB have also been described in the preoperative ECG of patients with tetralogy of Fallot.[2, 3] Also, it has been pointed out that when the ECG shows severe right ventricular hypertrophy the typical findings of LAH may be obscured by the presence of marked right axis deviation and only the initial 0.02 second vector may indicate the presence of a minor degree of the conduction abnormality.[7] Disagreement appears to exist, however, as to the frequency with which the 0.02 second vector is disturbed in LAH.[8]

In our surgical experience with cases of tetralogy of Fallot, we have found LAH and RBBB to occur in 7 per cent of cases postoperatively. The purpose of this paper is to determine the incidence of these conduction abnormalities preoperatively and also to determine whether minor evidence of LAH in the presence of right ventricular hypertrophy and right axis deviation predisposes to the subsequent development of LAH and RBBB or even complete heart block.

Materials and methods

Our material consists of 217 patients who were operated on for complete correction of tetralogy of Fallot. One hundred and thirty-three were male and 84 were female and their average age was 10 years. All patients were fully investigated by cardiac catheterization and angiography. This series does not include patients with tetralogy complicated by other malformations such as atrial septal defect, endocardial cushion defect, or unusual types of ventricular septal defect. Of the 217 operations, 184 (61

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Table I. Conduction abnormalities before surgery in 217 cases of tetralogy of Fallot (Group I)

Diagnosis	*No. of patients*	*% of patients*
Complete RBBB*	0	0
LAH†	0	0
Incomplete RBBB alone	22	10
Minor LAH	12	10
Minor LAH with incomplete RBBB	10	
Total incomplete RBBB	32	14.7

*RBBB = right bundle branch block.
†LAH = left anterior hemiblock.

Table II. Conduction abnormalities induced by surgery in 160 cases of tetralogy of Fallot (Group II)

Diagnosis	*No. of patients*	*% of patients*
LAH*	0	0
LAH with RBBB†	11	7
Complete RBBB	120	75
Incomplete RBBB	4	2.5
Total RBBB	135	84

*LAH = left anterior hemiblock.
†RBBB = right bundle branch block.

Table III. Relationship of preoperative minor left anterior hemiblock to postoperative left anterior hemiblock in 160 patients

Preoperative conduction defect	*No.*	*Postoperative LAHB* (No. cases)*	*% developing LAHB*
Minor LAHB	16	5	31
No LAHB	144	6	4
Total	160	11	7

*LAHB = left anterior hemiblock.

per cent) were performed by one surgeon, and in all cases the ventricular septal defect was described as being infracristal and of the usual size.

Twelve lead ECG's were available in all 217 patients preoperatively and in 160 of these ECG's were also available after operation. The latter tracing was available for examination at a mean interval of 17 months following operation. In the remaining 57 patients only rhythm strips were available in the postoperative period.

The material is divided into two groups.

Group 1. The entire group of 217 patients was used to analyze the conduction abnormalities preoperatively in uncomplicated cases of tetralogy of Fallot and to ascertain the incidence of postoperative complete heart block.

Group 2. The conduction abnormalities induced by surgery were analyzed in 160 of the 217 cases where both pre- and postoperative tracings were available.

Criteria for conduction abnormalities. Criteria for the diagnosis of conduction abnormalities were as follows:

1. *Left anterior hemiblock.* This was diagnosed when the mean QRS axis was deviated to the left at −30° or more. Particular attention was paid to the location of the 0.02 second vector in these cases.

2. *Right bundle branch block.* QRS duration of 0.12 sec. or more with a prominent S wave in standard Lead I and RSR in V_1. Incomplete RBBB was considered to be present when the QRS duration was 0.10 to 0.11 sec. The majority of our patients were in the 7 to 10 year age grou at which time the QRS duration is usuall between 0.07 to 0.09 sec.[10]

3. *Left anterior hemiblock and ri bundle branch block.* In the presence o RBBB three main vectors were plotte in the frontal plane from the scalar ECG according to the method of Grant.[11] Th first vector was plotted for the first 0.0 sec., the second for the intermediate por tion, and the third for the last 0.04 sec. LAH was considered to be present when th mid vector was located at −30° or furthe leftward. In these cases, as shown by Rosenbaum,[1] the QRS forces at 0.02 sec are located at +120° in the frontal plan and produce small q waves in Leads I and aVL and small r waves in Leads II and III. In the next 0.04 sec the mid vector points to the left at −30° or more resulting in

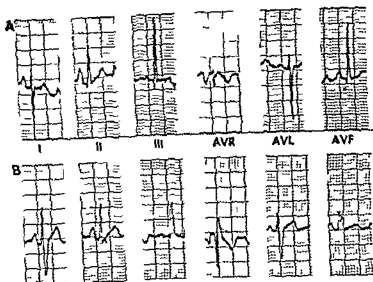


Fig 1 ECGs showing changes usually observed in tetralogy of Fallot *A* Preoperative tracing shows right axis deviation *B* Postoperative tracing showing complete RBBB There is no evidence of LAH in either tracing

deep S waves in standard Leads II III and aV_F The terminal forces resulting from RBBB point to the right at about $+180°$ [2,12]

4 *Minor left anterior hemiblock* This was considered to be present when in the presence of ECG evidence of severe right ventricular hypertrophy and marked right axis deviation small q waves were present in standard Leads I and aV_L associated with an rSR wave in Lead III and an rS or rSR wave in Lead II In the presence of RBBB this abnormality was similarly diagnosed when the first vector was located at $+120$ but without deviation of the mid vector to the left beyond $-30°$

Results

Preoperatively in Group I right axis deviation was present in 213 of the 217 cases and the mean QRS axis was found to be $+150°$ In the remaining 4 cases the QRS axis was normal The conduction abnormalities are detailed in Tables I and II Complete RBBB and LAH and the combination of these abnormalities were universally absent in the preoperative tracings Incomplete RBBB was *infrequent* and occurred in 7 *per cent* of the cases and a minor degree of LAH was *present* in 10 per cent of the cases

Postoperatively in Group II RBBB occurred in 84 per cent of the cases (Fig 1) and the combination of LAH and RBBB occurred in 7 per cent of the cases Of the 16 *patients with a minor* degree of LAH preoperatively 5 (32 per cent) developed LAH after operation (Fig 2) In the remaining 11 cases the mid vector displayed a slight leftward shift but not beyond $-30°$ (Fig 3) *Of the 144* patients who had *no evidence of LAH* at all before *operation* only 6 (4 per cent) developed LAH Of these 6 with postoperative LAH 3 *developed* a pattern without Q waves in Leads I and aV_L the major QRS *forces* however were deviated in a *pattern quite* typical of LAH (Fig 4) Evidence of LAH was thus present preoperatively in 5 of the 11 patients with surgically induced LAH

Complete heart block followed surgery in 2 of the 217 patients Neither patient had *evidence of* preoperative LAH In one case *heart block* was evident immediately *following* completion of the operation and has persisted for 7 years without Stokes Adams *attacks* In the second case, complete heart block occurred intermittently after operation subsequently there was a return to sinus rhythm with ECG evidence of LAH and complete RBBB This patient was recatheterized one year after surgery and during this procedure again developed temporary complete heart *block* Sinus

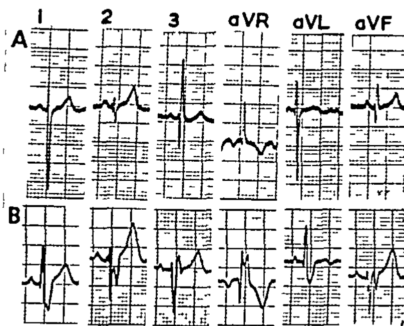


Fig 2 ECG showing A preoperative evidence of minor LAH in the presence of RAD The small q waves present in Leads I and aV_L and the small r waves in Leads III and aV_F indicate the 0 02 sec located at +120 Postoperatively the degree of LAH has increased with the mid vector located at about −100 in the presence of complete RBBB

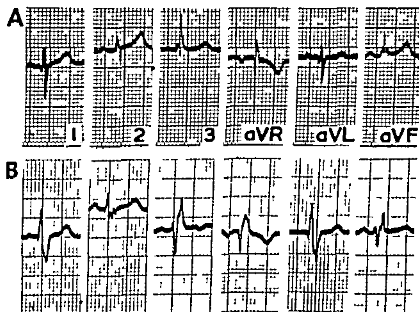


Fig 3 ECGs showing A preoperative evidence of a minor degree of LAH in the presence of right axis deviation and B postoperative tracing indicating complete RBBB The deeper S wave in S_3 and the taller R waves in aV_L and S_1 indicate a slight leftward shift of the mid vector but not beyond −30

rhythm then returned with evidence of LAH and complete RBBB Six years after operation complete heart block returned spontaneously and has remained as a permanent feature The occurrence of Stokes Adams attacks then necessitated implantation of a permanent transvenous pacemaker which has been utilized for the last three years

Commentary

Cases of tetralogy of Fallot with severe obstruction to pulmonary blood flow usually exhibit right axis shift of the mean QRS axis Thus Keith[13] (who studied 62 cases) and Burch and DePasquale[14] who studied 92 cases) found that all their cases showed marked to moderate right axis deviation A normal axis may be encountered

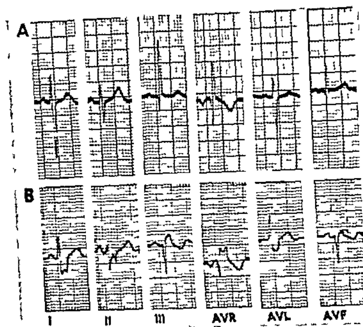


Fig 4 ECGs showing A preoperative right axis deviation without evidence of minor LAH B Post operative tracing shows complete RBBB and LAH There are no Q waves in Leads I and aV_L indicating absence of significant disturbance of 0 02 second vector

in cases with less obstruction to pulmonary blood flow but left axis deviation (LAH) is extremely rare and has a tendency to be associated with the pentalogy (tetralogy of Fallot with patent foramen ovale)[15] We have also encountered cases of pentalogy and cases of tetralogy with endocardial cushion defect with LAH but these cases have been excluded from the present series In an analysis of 136 patients with tetralogy Kulbertus Coyne and Hallidie Smith[2] found that 3 cases (2 2 per cent) manifested LAH In one of these cases the infracristal defect was unusually large and in the other two cases there were associated anomalies such as multiple muscular ventricular septal defects (VSD s) an abnormal tricuspid valve secundum atrial septal defect and rupture of a sinus of Valsalva These authors also found LAH and RBBB in a further 7 cases (5 2 per cent) In only one of these cases was the VSD of the usual infracristal variety in the remaining cases there was an endocardial cushion type of VSD multiple muscular VSDs or left ventricular-right atrial communication In our series of 217 cases of uncomplicated cases of tetralogy with the usual infracristal type of VSD the ECG was characterized by the absence of LAH RBBB and LAH combined with RBBB

It is apparent that in the uncomplicated form of tetralogy of Fallot LAH RBBB and LAH with RBBB are rare and that the presence of these conduction abnormalities indicates an unusual type of VSD or an additional malformation Recently Rosenbaum and associates[8] in their analysis of the ECG features of four patients with tetralogy of Fallot who developed postoperative LAH and RBBB pointed out that in the presence of severe right ventricular hypertrophy and right axis deviation small q waves in standard Leads I and aV_L and small initial r waves in Leads II III and aV_F are unusual and may possibly indicate the presence of a minor degree of LAH These findings have been in keeping with their previous observations that in the presence of severe right ventricular hypertrophy a small degree of LAH does not produce main QRS forces superiorly and to the left but instead only produces initial forces inferiorly to the right when there is marked right axis deviation[12] In LAH the QRS forces for the first 0 02 sec (which are orientated at approximately +120 in the frontal plane)

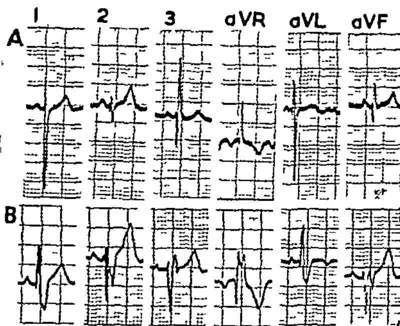


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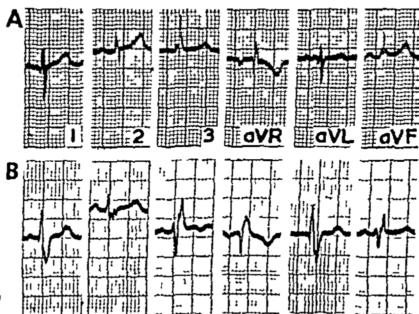


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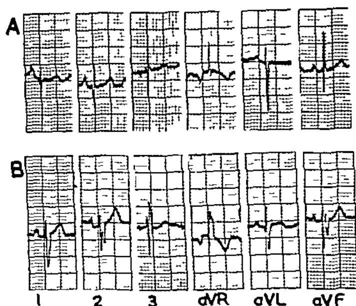


Fig 6 ECG showing *A* preoperative minor LAH and right axis deviation *B* Postoperative complete RBBB and shift of mid vector to the left typical of LAH

Dispute thus exists about the frequency of disturbance of the 0 02 second vector in LAH Our findings would indicate (even though the numbers are small) that the 0 02 second vector is usually disturbed and that when this finding is present preoperatively in the presence of marked right ventricular hypertrophy and right axis deviation there is an increased tendency to the development of LAH

The risk of developing LAHB following surgery is small (7 per cent) findings which are in agreement with those of Kulbertus Coyne and Halliday Smith[8] The prognosis for these patients will be answered by long term follow up since it is known that when LAH and RBBB are a result of ischemic heart disease or a sclero-degenerative process there is a strong tendency to develop complete heart block subsequently[14, 15] Our one patient who developed intermittent complete heart block then LAH and RBBB and finally stable complete heart block almost certainly had damage to the common bundle or the inferior division of the left bundle at the time of operation Immediate postoperative complete heart block occurred in less than 1 per cent of our cases and this experience is in accord with other series.[15]

Summary

The preoperative ECG was studied in 217 patients who underwent total surgical correction of uncomplicated tetralogy of Fallot and the effects of surgery were observed in 160 of these cases Analysis of the incidence of LAH RBBB and the combination of these conduction defects revealed that these were universally absent in the preoperative tracings their presence should therefore suggest the possibility of an unusual variety of VSD or an associated malformation RBBB was induced surgically in 84 per cent and the combination of RBBB and LAH was induced surgically in 7 per cent of cases In LAH the mid vector was located at $-30°$ or further to the left and in the majority of cases the 0 02 second vector was located at $+120°$ producing q waves in Leads I and aV_L Preoperatively 10 per cent of the tracings showed the presence of small q waves in Leads I and aV_L in the presence of right axis deviation (RAD) and it has been previously suggested that this represents a minor degree of LAH Our data would lend credence to this possibility because surgically induced LAH occurred in 31 per cent of these cases and in only 4 per cent of the cases where these findings were absent. In the patients

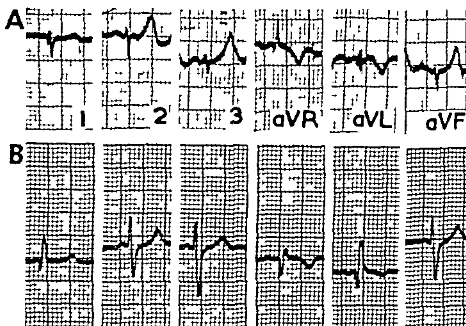


Fig 5 ECG showing A preoperative minor LAH in the presence of marked right RAD mean QRS axis about +210 B, Postoperative tracing shows LAH with mean QRS vector about −40

are a result of early activation of the posteroinferior wall of the left ventricle in an inferior and rightward direction and are responsible for the Q waves in Leads I and aV_L

These features were looked for in the preoperative ECG of our patients and found in 10 per cent of our tracings in the presence of right axis deviation One third of these patients subsequently developed LAH and RBBB with the mid vector then located to the left of −30° whereas this complication occurred in only 4 per cent of patients whose ECG s showed no evidence of hemiblock at all These findings would lend support to Rosenbaum s observations

Feldt DuShane and Titus[8] in their study of the anatomy of the conduction system in the tetralogy of Fallot found that 5 of their 78 autopsied cases of tetralogy had an ECG considered to be similar to that of the AV canal pattern This similarity lay in the fact that the initial QRS axis was directed inferiorly and to the right with q waves in Lead I and aV_L producing an initial counterclockwise loop with a mean QRS axis of −150°[8] In all these patients the VSD was of the usual infracristal type and it was noticed that there was a short distance between the AV node and the left bundle branches the effect of surgery on the ECG was not studied This ECG pattern is compatible with a minor degree of LAH as encountered in some of our cases (Fig 5) but usually in our case the mean QRS axis did not deviate so far to the right (Fig 6)

It would appear therefore, that typical LAH is rare but that a minor degree of of LAH in the presence of right axis deviation (RAD) may occur in uncomplicated tetralogy of Fallot and that following surgery in this type of case, the degree of hemiblock may increase postoperatively, and the main QRS forces may then point to the left The precise anatomy of the conduction system in these cases is not known but presumably the anterior division lies unusually close to the VSD so that surgery further damages the conduction tissues

Lemberg Castellanos and Arcebal[9] have recently observed that in LAH and RBBB the initial 0 02 second vector may be orientated to the left and superiorly and they have attributed this to myocardial and septal fibrosis findings which are in disagreement with those of Rosenbaum In of our 11 patients whose postoperative ECG s were otherwise compatible with LAH there was also no significant disturbance of the 0 02 second vector and Q waves were absent in Leads I and aV_L (Fig 4) This may possibly be a result of septal fibrosis significant postoperative septal rotation, or even a minor degree of left posterior hemiblock

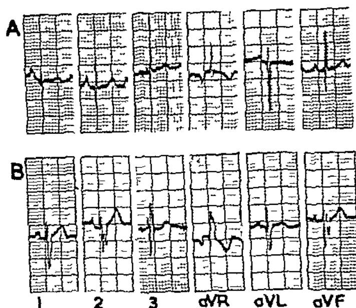


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with surgically induced LAH, evidence of a minor degree of LAH was present in half of these cases before operation

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Experimental and laboratory reports

Exchangeable potassium in heart disease Long-term effects of potassium supplements and amiloride

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There is general agreement that body potassium is reduced in patients with severe heart disease particularly when this is complicated by heart failure and the use of powerful potassium wasting diuretics While some workers believe that potassium depletion reflects loss of lean body mass alone others suggest that cellular depletion is also present

In an earlier study from this hospital Singh Hurley and North[1] compared values of total exchangeable potassium (Ke) in patients with heart disease with values from normal subjects reported in the literature They found that patients on diuretics had low values of Ke expressed as mEq Ke kg body weight (mEq of exchangeable potassium per kilogram of body weight) although all were on potassium supplements or spironolactone In a short term study they showed that the addition of the potassium sparing diuretic amiloride 20 mg daily to furosemide 80 mg daily resulted in a 35 per cent reduction in urinary loss of potassium

These observations have been extended in the present study which had two primary aims (1) to compare the Ke of control patients with heart disease who were not on diuretics with that of trial patients who were on diuretics and on potassium supplements and (2) to compare the relative efficacy of potassium supplements and amiloride in maintaining Ke over a relatively long period

Methods

Exchangeable potassium (Ke) was measured by isotope dilution using [42]K following the method of Flear and associates[2] who recommended a period of 24 hours for equilibration The tracer was given orally and after 24 hours the specific activity of four urine specimens passed at hourly intervals was measured in a Packard twin channel autogamma spectrometer Chemical measurements of serum and urinary potassium were made with an internal standard flame photometer No allowance was made for fecal loss of potassium which is generally less than 0 5 per cent of the administered dose[3] The mean of the four

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Table I. Comparison of control and trial patients

Control patients								Trial patients					
Patient No	Age (yr)	Sex	Wt (Kg)	Diagnosis	NYH	Ke/LBM (mEq/Kg)	Serum K+ (mEq/L)	Patient No	Age	Sex	Wt (Kg)	Diagnosis	NYH
1	47	M	63.5	AVD*	2	60.5	4.2	1	50	F	80.0	MVD	3
2	49	M	69.0	IHD*	4	55	4.0	2	43	F	73.7	AVD	4
3	20	M	76.5	AVD	2	65.5	4.0	3	53	F	58.6	MVD	3
4	61	M	67.5	IHD	4	51.8	3.9	4	56	M	51.7	AVD	3
5	55	F	54.7	AVD	3	60.5	3.8	5	66	M	78.1	MVD	2
6	40	M	67.1	IHD	4	62.5	3.9	6	44	F	55.3	MVD	3
7	46	M	72.1	IHD	4	51.5	4.2	7	66	F	69.7	MVD	4
8	49	M	64.5	AVD	3	55	4.4	8	62	M	62.9	MVD	2
9	43	M	68.6	IHD	4	—	3.9	9	28	F	65.5	AVD	4
								10	51	F	55.4	MVD	3
								11	35	F	54.1	MVD	3

*Abbreviations: AVD = aortic valve disease; IHD = ischemic heart disease; MVD = mitral valve disease; NYH = New York Heart Association classification. Details of serum K+ and Ke/LBM values for trial patients are shown in Table IV.

estimates of Ke was taken for each patient, the average deviation from the mean value for individual estimates being 3.9 per cent (S.D. = 3.3 per cent). Results were accepted only if serial estimates showed that equilibrium had been reached and results were excluded from one patient who did not reach equilibrium.

The expression mEq Ke/Kg body weight does not make adequate allowance for the loss of lean body mass in disease states. For this reason Ke is expressed in this study as mEq Ke/Kg lean body mass. This expression has the advantage that it also allows for the difference in fat mass between males and females.

Total body water (TBW) was measured by the sampling of both urine and plasma five hours after an oral dose of 500 μCi of tritiated water. Samples were assayed in a Packard liquid scintillation spectrometer. Values of TBW calculated from urine and plasma samples showed good correlation ($r = 0.91$), and the average of the two values was used for all calculations. Lean body mass (LBM) was calculated from the formula[4]

$$LBM = \frac{TBW}{73 \text{ per cent}}$$

Red cell potassium (K_{RBC}) was measured by the method of Singer and colleagues.[5] Blood urea, serum sodium, CO_2 content, creatinine, uric acid, one hour postprandial blood glucose, bilirubin, S.G.O.T., and alkaline phosphatase were measured with a Technicon autoanalyzer. Normal values for uric acid in our laboratory are: Females = 3.2 to 7.2 mg per cent; Males = 3.7 to 8.3 mg per cent. For comparison K_{RBC} and serum potassium were measured in 50 normal staff members. The mean value of K_{RBC} for this group was 97.2 mEq per liter (S.D. = 4.6 mEq per liter); the value for males was 94 mEq per liter and for females 98.4 mEq per liter. The mean value for serum potassium was 4.2 mEq per liter (S.D. = 0.3 mEq per liter).

Patients

There were nine control patients, eight of whom were men. Five of these patients had ischemic heart disease and four had valvular disease. One patient only was receiving digitalis and two patients were taking propranolol. There were eleven trial patients, eight of whom were women. All had severe valvular disease and ten were on treatment with digitalis, furosemide 80 mg, and potassium supplements 48 mEq daily given as potassium chloride (Slow K). One patient (No. 5) was on digitalis, furosemide 40 mg, and potassium chloride 32 mEq daily. All patients were on this therapy for a minimum of three months before the start of the trial, the mean period being 2.1 years.

Table II Comparison of control and trial patients (mean values)

	No of patients	Age (yr)	Wt (kg)	Dietary K (mEq/Kg)§	TBW/Wt* (%)	Serum K+ (mEq/L)	Ke/LBM† (mEq/Kg)‡	Serum Na+ (mEq/L)	Serum creatinine (mg %)	Uric acid (mg %)
Control	8	43	67.1	81	61	4.0	57.8	137	1.2	8.4
Trial	11	51	63.1	[illegible]8§	58	3.9	51.6	140	1.1	9.5

*TBW = total body water
†LBM = lean body mass
‡Difference between control and trial patients = $0.05 > P > 0.01$
§Does not include potassium supplements.

The two groups were well matched for symptomatic limitations dietary intake of potassium body weight and lean body mass Age distribution was similar and no patient was obese

Design of study

Comparison of control and trial patients (Tables I and II) Ke/Kg lean body mass serum potassium K_{RBC} and other biochemical values were measured in control patients (not on diuretics) and in trial patients (on diuretics and potassium supplements)

Comparison of the efficacy of potassium supplements and amiloride in maintaining Ke in trial patients For two months after the initial measurements trial patients were maintained on furosemide and potassium supplements and measurements were repeated at the end of this period Amiloride was then substituted for potassium supplements Three patients were given 15 mg daily for two weeks and then changed to 10 mg daily and the remaining eight patients were given 10 mg daily from the outset Two months later measurements were again repeated Dietary potassium clinical status body weight skin fold thickness and biochemical indices were recorded at intervals throughout the study Differences between control and trial groups were assessed by the unpaired t test and changes throughout the study in the trial group were assessed by the paired t test

Results

Comparison of control and trial patients (Table II) The mean value for Ke in control patients was 57.8 mEq/Kg lean body mass (LBM) This is comparable with

Table III Stability of trial patients (mean values)

Study period	Mean body wt (Kg)	Mean lean body mass (Kg)
1*	63.5	50.4
2†	63.9	49.5
3‡	64.2	50.7

*Measurements made after a run in period on digitalis furosemide 80 mg and Slow K 48 mEq daily One patient received furosemide 40 mg and Slow K 32 mEq
†Measurements made after a further 2 months on this therapy
‡Measurements made after 2 months on digitalis furosemide 80 mg and amiloride 10 mg daily

values of 60 to 62 mEq/Kg LBM found in normal subjects of both sexes[6,7] The mean value of 51.6 mEq/Kg LBM in trial patients was significantly lower ($0.05 > P > 0.01$)

Serum potassium and K_{RBC} values were similar in the two groups and serum sodium was slightly higher in the trial group The differences in serum uric acid did not achieve statistical significance and all other biochemical values were similar in the two groups

Comparison of the effects of potassium supplements and amiloride in maintaining Ke in trial patients Changes throughout the study periods are summarized in Tables III and IV and in Figs 1 and 2 No patient had overt evidence of fluid retention Clinical status weight and lean body mass were stable in all patients throughout the trial period There was no significant change in Ke over the study period indicating that body stores of potassium were maintained adequately while on treatment with amiloride There was a

Table IV. Serial changes in trial patients

Patient No	Serum K (mEq/L)			Ke/LBM* (mEq/Kg)			K_{RBC} (mEq/L)			Serum uric acid (mg/100 ml)		
	Study period			Study period			Study period			Study period		
	1	2	3	1	2	3	1	2	3	1	2	3
1	3 6	3 7	4 0	40 6	43 0	55 3	94	97	102	8 6	11 7	8 4
2	3 4	3 5	3 6	50 6	46 7	50 8	99	99	100	8 6	15 6	8 6
3	3 4	3 7	4 1	45 9	58 0	44 5	97	100	94	9 0	9 4	7 1
4	3 9	3 7	4 1	59 1	60 8	42 0	100	93	97	12 0	10 8	8 9
5	4 7	4 4	4 3	53 2	50 6	56 4	101	107	105	10 2	12 9	9 3
6	3 9	4 0	4 0	59 2	53 4	47 5	93	96	94	10 3	8 5	7 [illegible]
7	—	3 6	3 9	—	46 9	46 3	—	93	92	—	7 6	9 4
8	4 2	4 3	5 9	47 0	60 6	43 4	90	105	91	7 9	10 2	7 1
9	4 2	3 5	4 2	53 0	45 1	49 0	96	102	97	11 7	14 0	8 0
10	4 1	3 8	3 6	51 8	37 2	32 3	92	105	92	6 7	8 6	6 1
11	3 6	3 5	4 4	55 9	53 5	58 2	100	96	95	10 3	9 3	6 4

*Lean body mass

slight but significant rise in serum potassium following treatment with amiloride but no change in K_{RBC}

There was a significant fall in serum uric acid levels following treatment with amiloride. No changes were seen in blood urea, serum sodium, CO_2 content, creatinine, serum bilirubin, S G O T, alkaline phosphatase, or one hour postprandial blood sugar.

The relationships between serum potassium and Ke and between K_{RBC} and Ke are shown in Figs 3 and 4. Values for patients in both control and trial groups are included but K_{RBC} values were available in only three patients in the control group. No correlation was shown; the correlation coefficient for serum potassium/Ke was 0 17 and for K_{RBC}/Ke was 0 24. Correlation was not improved by combining values for serum potassium and K_{RBC} and comparing them with Ke by multiple regression.

Side effects. No side effects were reported by any of the patients, who generally preferred amiloride to potassium supplements. However, one patient with severe multivalvular disease treated for 2 years with digitalis and diuretics died at the time of admission for final assessment (patient No 9, Tables I and IV). Multiple ventricular ectopic beats had been present for five months before the trial began and were not abolished by lowering digoxin dosage. Four months before the trial, the patient suddenly lost consciousness while watching television. The episode lasted about five minutes and may well have been due to a ventricular arrhythmia. Throughout the trial serum potassium and Ke values showed only random changes. During her final admission she developed ventricular fibrillation. Sinus rhythm was restored but idioventricular arrhythmias recurred and the patient died 24 hours later despite resuscitative measures. It was considered that death was related to severe underlying heart disease and it appeared unlikely that amiloride administration was a factor.

Discussion

In the past, measurements of body potassium have been made either with the whole body counter or by calculating Ke. Surveyer and Hughes[3] considered the whole body counter more accurate, but in their study only single measurements of Ke were made, a procedure strongly criticised by Hear and colleagues. These authors accepted that radioactive potassium was distributed among some 85 per cent of the body's potassium after 24 hours, which they considered the optimum period of

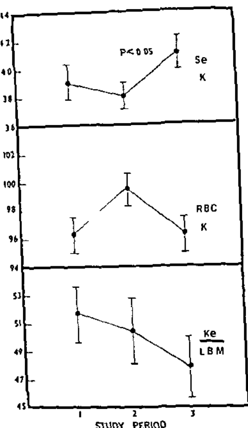


Fig *1* Changes in serum potassium (mEq /L) Kase (mEq /L) and Ke(mEq /Kg LBM) in trial patients during the study periods The only change to achieve statistical significance was the change in serum potassium between measurements 2 and 3 The change in Ke between measurements 1 and 3 was not significant Bars show mean values ± 1 SEM

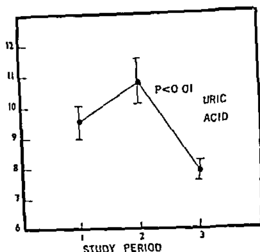


Fig *2* Changes in blood uric acid (mg /100 ml) in trial patients during the study period The changes between measurements 2 and 3 and between measurement 1 and 3 were both significant (0 01 > P > 0 001)

equilibration Although the method is subject to the errors inherent in radioactive laboratory procedures the accumulated evidence argues that results obtained are physiologically meaningful Previous work indicates that the best assessment of body potassium is to consider the results obtained in relation to the subject s LBM as determined by measurement of TBW [4] Because body potassium and LBM fall proportionately in wasting disease a reduction in Ke Kg LBM implies cellular loss of potassium

Body potassium is reduced in patients with severe heart disease especially when associated with heart failure[6] and with the use of potassium wasting diuretics [9] Some workers[9, 10] believe that the reduction of body potassium results from the wasting of lean body mass without additional cellular potassium depletion Others have argued that cellular depletion of potassium is present [11, 12] predisposing to arrhythmias induced by digitalis or following heart surgery [12] Sometimes either conclusion can be drawn from the data! For example White and associates[10] studied Ke in 42 patients with severe valvular heart disease the majority of whom were on diuretics Results were expressed in terms of predicted values for height based on the regression equation of Flear and co workers [2] Ke values were lower than predicted normal values but on the basis of additional data on body water and sodium it was concluded that the potassium deficiency was related to loss of cell mass rather than to cellular depletion of potassium Figures of Ke/Kg LBM calculated from White s data[10] were 46 mEq /Kg (males) and 47 mEq /Kg (females) compared with normal values of 60 to 62 mEq /Kg [6, 7] This reduction in values of Ke/Kg LBM implies cellular potassium depletion contrary to the views expressed by the authors Subsequently White[14] demonstrated a significant increase in exchangeable potassium following treatment with potassium supplements

In the present study control and trial

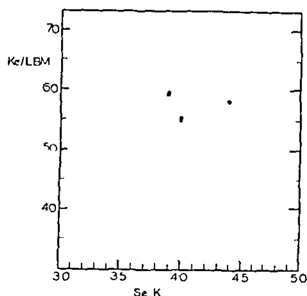


Fig. 3. Relationship between serum potassium (mEq./L.) and Ke/LBM (mEq./Kg.). Values are plotted for both control and trial patients.

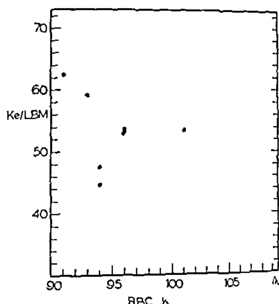


Fig. 4. Relationship between K_{RBC} (mEq./L.) and Ke/LBM (mEq./Kg.).

groups were well matched except for the difference in sex distribution. Use of LBM allows for differences in the proportion of body fat in males and females and normal values for Ke/Kg. LBM are similar in both sexes.[6,7] The variation in sex distribution should not, therefore, affect results.

All control patients had significant symptoms but were free of heart failure. As a group they did not show a reduction of Ke/Kg. LBM although this observation does not deny the possibility that some patients may be so affected. By contrast, trial patients on diuretics showed a reduction in Ke/Kg. LBM despite full potassium supplements. It was concluded that cellular depletion of potassium was present in patients receiving diuretics but was not usually found in cardiac patients who were not receiving diuretics.

Values for TBW were higher than normal values reported in the literature, suggesting that our patients may have shown an occult increase in extracellular fluid. This would appear unlikely, however, since lower values for TBW (and hence LBM) would give values for Ke/Kg. LBM well above normal in control patients. Whatever the explanation for this observation, differences in TBW do not appear responsible for differences in Ke/Kg. LBM between control and trial patients, since average values for TBW/body weight in control patients (61 per cent) were similar to those in trial patients (58 per cent). Differences between males and females are too small to affect these values significantly.

Amiloride in a dosage of 10 mg. daily was free of side effects, the single death being considered unrelated. With two months therapy there was a small but significant rise in the mean value of serum potassium and a modest fall in Ke/Kg. LBM which did not achieve statistical significance. This dose appeared approximately equivalent to 48 mEq. of potassium chloride daily in maintaining body potassium, but a higher dose would be required to increase Ke. The dose of 10 mg. was chosen to avoid excessive diuretic action by the combined regimen in patients already free of heart failure. No harmful effects on renal or liver function or on blood glucose levels were demonstrated with amiloride therapy and there was no abnormal elevation of serum potassium.

High levels of serum uric acid in trial patients were presumably related to therapy with furosemide. Reduction of uric acid levels after the administration of amiloride is of considerable interest. In short-term studies patients taking amiloride alone usually showed no change[15] or a fall[16] in serum uric acid with no change in uric acid clearance. In long-term studies small groups of patients taking amiloride

in conjunction with thiazides or other proximally acting diuretics showed variable changes in serum uric acid some showing a rise some a fall[17] and some no change[18] Differences in therapy and in clinical status preclude firm conclusions from these studies

Furosemide induced hyperuricemia is poorly understood[19] It may result from volume contraction from the induction of raised lactic acid levels which lead to the suppression of tubular secretion of uric acid or from a change in the intra/extra *cellular distribution* of uric acid The majority of uricosuric agents are organic acids with the exception of zoxazolamine[20] Amiloride hydrochloride is the salt of a moderately strong base and it seems unlikely that it has a direct uricosuric effect in lowering uric acid levels in patients who are taking furosemide Further exploration of this effect on serum uric acid is indicated

As found in previous studies correlation between serum potassium and Ke was poor Certainly low values of serum potassium were always associated with low values of Ke but low values of Ke were frequently found with normal values of serum potassium Similarly correlation between K_{RBC} and Ke was poor This contrasts with conclusions of others who have suggested the K_{RBC} may be useful in predicting body stores of potassium[3,21] No such prediction was possible over the range of values shown by our patients Correlation with Ke was not improved by taking into account both serum potassium and K_{RBC}

Summary

Patients with heart disease not requiring treatment with diuretics did not show depletion of body potassium expressed as Ke/Kg LBM Patients treated with furosemide (80 mg daily) and potassium supplements (48 mEq daily) were depleted of potassium Treatment with 10 mg of amiloride daily was as effective as 48 mEq of potassium supplements in maintaining body potassium No side effects of the drug were noted but there was a significant reduction in serum uric acid after two months on the combined regimen of furosemide and amiloride No useful correlation was found between serum potassium or red cell potassium and Ke

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A critical examination of the validity of the use of vein grafts in treating ischemic heart disease

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Over the last thirty years numerous surgical procedures have been developed for the revascularization of the ischemic myocardium. At present aortocoronary artery bypass grafts are being used clinically to treat cases of ischemic heart disease.[1-6]

This treatment is based on experimental studies with animals. In these studies sudden complete (acute) ligation of one of the major coronary arteries is followed by the anastomosis of a systemic artery and the peripheral coronary artery distal to the ligation. These cases demonstrate a significant blood flow directly to the coronary beds. The oxygenated bypassed blood protects the myocardium of the ligated coronary area from acute ischemic changes.

These data have been used as a rationale to support the use of aortocoronary bypass grafts in numerous clinical cases.[2-6] In most ischemic heart disease patients, however, coronary stenoses or occlusions develop much more slowly than in the experimental animal. Even if the coronary occlusion developed suddenly, the corrective operation was not undertaken in the acute stage; rather, bypass grafts were usually inserted six or more months after the onset of acute occlusion.

To make the experiment more similar to clinical cases, the left circumflex coronary artery of each dog was ligated. The dogs were then kept alive in this state for six months. After this period, the coronary artery distal to the ligation was then anastomosed to a systemic artery. The results of blood flow studies performed after this delayed operation differed greatly from those described in the literature in which the aortocoronary anastomosis occurred soon after the coronary ligation. In this paper the authors carried out systemic to coronary anastomosis experimentally and measured the blood flow in the bypass grafts in both acute and chronic stages.

Materials and methods

Acute experiments. Five mongrel dogs weighing 18 to 22 kilograms were anesthetized by the intravenous injection of sodium pentobarbital. Respiration was maintained through an endotracheal tube attached to a Bird respirator. The chest was opened through the left fourth intercostal space. The pericardium was incised anterior to the left phrenic nerve, and the left circumflex coronary artery close to the origin was dissected free. The left subclavian artery was dissected from the aortic arch to its first branch and then transected. Aortic pressure was recorded through a catheter in

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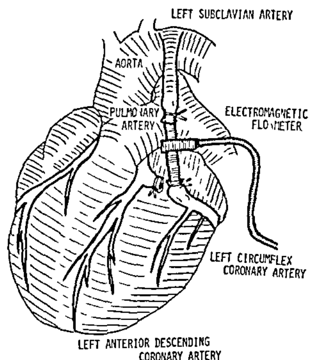


Fig 1 Schematic drawing showing the left subclavian artery anastomosed to the left circumflex coronary artery distal to the ligature The electromagnetic flow probe is 2 mm in internal diameter The bypass connecting tube is 7 cm in length

serted retrogradely from the femoral artery The tip of the catheter remained in the aortic arch Pulmonary artery pressure was recorded by another catheter inserted directly into the main pulmonary trunk

The circumflex coronary artery was ligated 1 0 cm from the bifurcation A small catheter 0 2 cm in diameter was inserted into the distal end of the circumflex coronary artery, and the peripheral coronary artery pressure was measured The pressures of the aorta the pulmonary artery, and the peripheral circumflex artery were recorded simultaneously As soon as the measurements of the distal coronary pressure were completed the bypass between the left subclavian artery and the peripheral coronary artery was established as shown in Fig 1 An electromagnetic flow probe 2 0 mm in diameter (MF 25 Nihon Kohden Kogyo Co, Ltd Tokyo Japan) was placed in the bypass circuit The total length of the bypass was 7 cm Flow measurements were continued for two hours following the insertion of the bypass

Chronic experiments In the chronic experimental series, the same anesthesia and thoracotomy procedures were used as in the acute series In five animals the left circumflex coronary artery was ligated 1 0 cm from the bifurcation

The dogs were kept alive for six month At this time they were anesthetized in preparation for surgery of the aortocoronary anastomosis Prior to anastomosis of the left subclavian artery to the peripheral coronary artery distal to the ligature the peripheral circumflex coronary pressure was recorded with the simultaneous tracings of aortic pressure pulmonary pressure and electrocardiogram (ECG) of the second standard limb lead In this chronic experimental series, a bypass circuit identical to the one used in the acute series was utilized (Fig 1) Flow measurements were recorded continuously for two hours following the establishment of the bypass

Results

In the five cases of the acute experimental series, the peripheral coronary artery pressure distal to the ligature was 30 mm Hg—almost 25 per cent of the systemic blood pressure (Table I, Fig 2) Because of this marked pressure difference between the aorta and the peripheral circumflex coronary artery, the flowmeter in the bypass circuit recorded a significant blood flow to the coronary vascular beds (Fig 3) The aortocoronary bypass flow was remarkably high immediately following the insertion of the bypass because the myocardial ischemia induced during the pressure measurements reduced coronary vascular resistance distal to the anastomosis

After the establishment of the aortocoronary anastomosis the ischemic myocardial area became hyperemic This condition continued for approximately ten minutes The aortocoronary flow gradually decreased to an average level of 38 ml per minute Once the blood flow reached this level it remained constant for two hours

In the chronic experimental series the peripheral coronary pressure increased markedly to a level approximately equal to the systemic blood pressure The systolic pressure of the peripheral circumflex coronary was at least 55 mm Hg The systolic pressure difference between the aorta and the peripheral circumflex coronary was approximately 10 mm Hg (Table II) Therefore the aortocoronary bypass graft

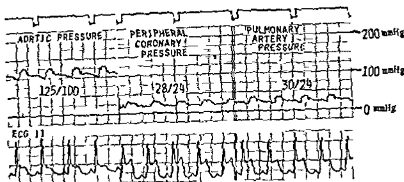


Fig. 2 Pressure recordings in Dog No. VG 27. Immediately following the ligation of the circumflex coronary artery the peripheral artery pressure is markedly low in comparison with the aortic pressure. ECG II shows the remarkable ST elevations

Table I Data from acute experiments

Dog No	Aortic pressure (mm Hg)	Peripheral circumflex coronary pressure (mm Hg)	Pulmonary artery pressure (mm Hg)	Systemic to-coronary flow (ml /min)
VG-22	110/85	30/20	30/22	35
VG 24	147/113	26/18	30/22	36
VG-25	160/134	34/28	22/15	40
VG 26	120/100	22/18	25/20	30
VG-27	125/100	28/24	30/24	50

Table II Data from chronic experiments

Dog No	Aortic pressure (mm Hg)	Peripheral circumflex coronary pressure (mm Hg)	Pulmonary artery pressure (mm Hg)	Systemic to-coronary flow (ml /min)
VG-1	100/80	8 /72	25/14	0
VG-i	120/100	110/95	28/20	5 0
VG-9	140/110	120/90	30/20	6 0
VG 11	108/90	98/83	25/15	10 0
VG-16	130/105	104/94	20/12	0

could not supply a significant amount of blood to the peripheral coronary beds in the chronic series (Fig 4). Flowmeter recordings showed an average flow of only 4 ml per minute. The blood flow in the chronic series was significantly less than the aortocoronary flow in the acute experimental series

Discussion

Many experimental reports concerning the systemic-to-coronary anastomosis strongly support the efficacy of the bypass graft. But these experiments were carried out under acute experimental conditions which did not consider changes in the peripheral coronary artery pressure after coronary stenosis. Although in acute cases the ligation of the major coronary artery initially induces low peripheral coronary pressure, the low peripheral pressure starts to increase slowly. The peripheral coronary pressure distal to the ligature can rise to the aortic pressure level[7]. It may be controversial to correlate pressure directly with collateral flow, nevertheless many articles

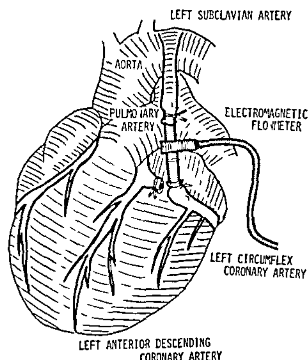


Fig. 1. Schematic drawing showing the left subclavian artery anastomosed to the left circumflex coronary artery distal to the ligature. The electromagnetic flow probe is 2 mm. in internal diameter. The bypass connecting tube is 7 cm. in length.

serted retrogradely from the femoral artery. The tip of the catheter remained in the aortic arch. Pulmonary artery pressure was recorded by another catheter inserted directly into the main pulmonary trunk.

The circumflex coronary artery was ligated 1.0 cm. from the bifurcation. A small catheter 0.2 cm. in diameter was inserted into the distal end of the circumflex coronary artery, and the peripheral coronary artery pressure was measured. The pressures of the aorta, the pulmonary artery, and the peripheral circumflex artery were recorded simultaneously. As soon as the measurements of the distal coronary pressure were completed, the bypass between the left subclavian artery and the peripheral coronary artery was established as shown in Fig. 1. An electromagnetic flow probe 2.0 mm. in diameter (MF 25, Nihon Kohden Kogyo Co., Ltd., Tokyo, Japan) was placed in the bypass circuit. The total length of the bypass was 7 cm. Flow measurements were continued for two hours following the insertion of the bypass.

Chronic experiments. In the chronic experimental series, the same anesthesia and thoracotomy procedures were used as in the acute series. In five animals, the left circumflex coronary artery was ligated 1.0 cm. from the bifurcation.

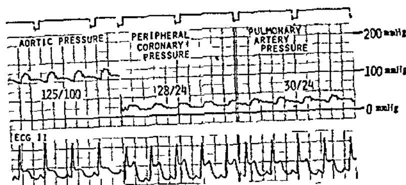
The dogs were kept alive for six months. At this time they were anesthetized in preparation for surgery of the aortocoronary anastomosis. Prior to anastomosis of the left subclavian artery to the peripheral coronary artery distal to the ligature, the peripheral circumflex coronary pressure was recorded with the simultaneous tracings of aortic pressure, pulmonary pressure, and electrocardiogram (ECG) of the second standard limb lead. In this chronic experimental series, a bypass circuit identical to the one used in the acute series was utilized (Fig. 1). Flow measurements were recorded continuously for two hours following the establishment of the bypass.

Results

In the five cases of the acute experimental series, the peripheral coronary artery pressure distal to the ligature was 30 mm. Hg—almost 25 per cent of the systemic blood pressure (Table I, Fig. 2). Because of this marked pressure difference between the aorta and the peripheral circumflex coronary artery, the flowmeter in the bypass circuit recorded a significant blood flow to the coronary vascular beds (Fig. 3). The aortocoronary bypass flow was remarkably high immediately following the insertion of the bypass because the myocardial ischemia induced during the pressure measurements reduced coronary vascular resistance distal to the anastomosis.

After the establishment of the aortocoronary anastomosis, the ischemic myocardial area became hyperemic. This condition continued for approximately ten minutes. The aortocoronary flow gradually decreased to an average level of 38 ml. per minute. Once the blood flow reached this level, it remained constant for two hour

In the chronic experimental series, the peripheral coronary pressure increased markedly to a level approximately equal to the systemic blood pressure. The systolic pressure of the peripheral circumflex coronary was at least 85 mm. Hg. The systolic pressure difference between the aorta and the peripheral circumflex coronary was approximately 10 mm. Hg (Table II). Therefore, the aortocoronary bypass graft



i 2 Pres ure recordings in Dog No. VG-27 Immediately following the ligation of the circumflex coronary tery the peripheral artery pres ure is markedly low in compari on with the aortic pressure *ECG II* hows the :markabl ST elevations

Table I Data from acute experiments

Dog No	Aorti pressure (mm Hg)	Peripheral circun flex coronary pressure (mm Hg)	Pulmonary artery pressure (mm Hg)	Systemic to-coronary flow (ml /min)
VG-2?	110/85	30/20	30/2?	35
VG-?4	147/113	26/18	30/??	36
VG-?5	160/134	34/28	2?/15	40
VG-?6	1?0/100	22/18	25/20	30
VG-27	1?5/100	28/24	30/?4	50

Table II Data from chronic experiments

Dog No	Aortic p essu e (mm Hg)	Peripheral circumflex coronary pressure (mm Hg)	Pulmonary artery pressure (mm Hg)	Systemic to-coronary flow (ml /min)
VG-1	100/80	85/7?	25/14	0
VG-7	120/100	110/95	28/?0	5 0
VG-?	140/110	120/90	30/20	6 0
VG-11	108/90	98/88	25/15	10 0
VG-16	130/10?	104/94	?0/1?	0

could not supply a significant amount of blood to the peripheral coronary beds in the chronic series (Fig 4) Flowmeter re cordings showed an average flow of only 4 ml per minute The blood flow in the chronic series was significantly less than the aortocoronary flow in the acute experi mental series

Discussion

Many experimental reports concern ing the systemic to coronary anastomosis strongly upport the efficacy of the bypass graft But these experiments were carried out under acute experimental conditions which did not consider changes in the peripheral coronary artery pressure after coronary stenosis Although in acute cases the ligation of the major coronary artery initially induces low peripheral coronary pressure the low peripheral pressure start to increase slowly The peripheral coronary pres ure de t il to the ligature can rise to the aortic pressure level[7] It may be con troversial to correl ite pressure and ... collateral flow nevertheless ...

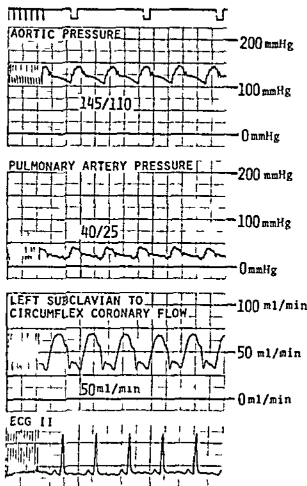


Fig 3 Systemic to-coronary flow studies in Dog No VC 27 (the same case as in Fig 2) The left subclavian artery has been anastomosed to the left circumflex coronary artery The mean blood flow is 50 ml per minute Elevated ST segments return to the base line after the establishment of the anastomosis

clearly describe a significant increase of the peripheral coronary pressure This increase is always demonstrated within a couple of weeks following the acute or chronic ligation of the coronary arteries [8, 11] Therefore in chronic cases a significant flow cannot be realized by the anastomosis of the peripheral coronary artery to the systemic artery In our chronic experimental series the aortocoronary flow averaged only 4 0 ml per minute This represents a maximum flow rate for these animals because no thrombosis, no stricture formation, and no histologic degeneration developed Such developments might occur to some extent over a longer period of time this would tend to decrease the initial flow rate of the anastomosed channel

Postoperative angiographic studies may demonstrate that radiopaque materials travel from the aorta to the coronary artery through the venous bypass grafts in experimental as well as in clinical cases Since the angiographic patency does not always indicate the presence of sufficient blood flow but only indicates anatomical continuity, the results of the angiographic studies do not serve as valid proof of physiologically functioning blood flow

Judging from animal experiments venous bypass grafts can be very effective if they are performed immediately after sudden and complete occlusion of the coronary artery In such cases the peripheral coronary pressure distal to the acute occlusion is still fairly low in comparison with the aortic blood pressure However, the surgical treatment described in clinical reports differs considerably from that used in the animal experiments in the former the time period between the occlusion and the operation was usually much longer [3, 5]

The flow studies in clinical cases done by some reporters[3, 6] describe considerable flow right after the bypass procedure Thus a significant discrepancy exists between our chronic experiment and these clinical reports In the cases in which the coronary arteries are not totally occluded, surgical procedures of those arteries might have induced to some extent ischemic myocardial changes If this is so then the initial flow following the insertion of the bypass would be reasonably high because of the reduced myocardial vascular resistance In these instances the constancy of the aortocoronary flow rate should be checked by observing it for at least 15 minutes after the operation

Summary

Bypass grafts can carry blood from the aorta to the coronary arteries if the grafts are performed immediately following coronary occlusion However the grafts cannot carry any significant amount of blood if the coronary arteries have been occluded for a long period of time before the operation because the peripheral coronary artery pressure distal to the occlusion will already have increased to the aortic pressure level Therefore the use of venous bypass grafts

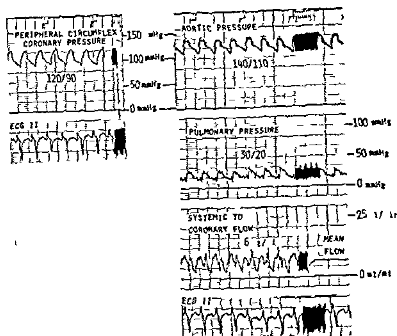


Fig 4 Pressure and flow recordings in Dog No VG 9 Six months after the ligature of the left circumflex coronary the peripheral coronary artery pressure is 120/90 mm Hg while the aortic pressure is 140/110 mm Hg The pres ure difference between the aorta and the peripheral coronary is only 20 mm Hg Accordingly the anastomosis of the left subclavian artery to the peripheral coronary artery reveals the bypass blood flow to be only 6 ml per minute

should be restricted to those acute conditions in which the operation can be performed immediately following sudden coronary occlusions

The authors wish to express their appreciation to Mr Michael Reich for his editorial as istance

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Angina pectoris and slow flow velocity of dye in coronary arteries—A new angiographic finding

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It has been classically stated that coronary arteriosclerosis, arterial hypertension, and valvular heart disease form the basic etiologic substrates of all cases of angina pectoris.[1] Simply stated, anginal pain is a reflection of an ischemic myocardium. However, the routine use of selective coronary arteriography has partially uncovered the complexity of the anginal syndrome and we have become fully aware of the fact that typical angina may be present without angiographic evidence of coronary arteriosclerosis. Various theories have been postulated for the underlying mechanism such as functional spasm, small vessel disease, abnormal oxygen hemoglobin dissociation, and myocardial cellular metabolic disturbances.[2,3]

The purpose of this paper is to describe a new cinearteriographic feature, related to slow flow velocity of angiographic dye in 6 patients with the anginal syndrome and normal coronary arteries.

Materials and methods

Four of the 6 subjects were clinically presumed to have coronary artery disease in light of a history of classical attacks of angina and electrocardiographic (ECG) changes, either at rest or after exercise. The two remaining subjects had atypical chest pain and epigastric pain. None had valvular heart disease, hypertension, pulmonary disease, thyrotoxicosis, collagen disorder, diabetes mellitus, or anemia.

The laboratory investigations included blood count, fasting blood sugar, blood urea nitrogen, cholesterol, uric acid, calcium, phosphorus, serum proteins, serum enzymes, triglycerides, serologic tests, urinalysis, x-ray, and fluoroscopic studies of the heart for size and configuration. Resting ECG, phonocardiogram, and vectorcardiogram (VCG) were also completed. All 6 patients had an exercise tolerance test.

Right and left cardiac catheterization was carried out in the supine position and pressures were recorded with Statham strain gauge multichannel on an Electronics for Medicine recorder. Cardiac output was computed by the indicator dilution technique using the Lexington computer. Left ventricular function was assessed in terms of cardiac index, stroke

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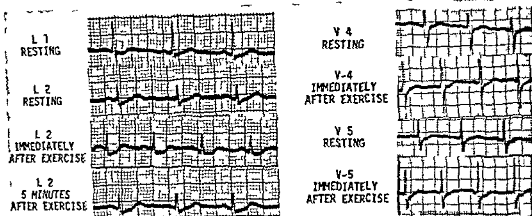


Fig 1 Positive exercise tolerance test in a patient with normal selective coronary arteriographs who displayed slow dye flow

Table I Physical and hemodynamic values in six patients with anginal syndrome and normal coronary arteries

Case no	*Heart rate (beats per min)*	*Aortic pressure (mm Hg)*	*R.A* mean values (mm Hg)*	*Cardiac index (L/M²)*	*Stroke index cc/beat/M²*	*LVEDP† (resting) (mm Hg)*	*LVEDP† (exercise) (mm Hg)*	*Aortic (% O₂ sat)*
1	54 60	75 50 to 100/60	5	2 3	38 3	12	15	94
2	83	90/70	4	3 8	52	5	rate 140 no exercise	96
3	55	130/75	5	2 7	38	15	15	94
4	62	130/70	3	4 3	49	7	17	95
5	71	90/65	6	3 5	49	7	8	95
6	110	100/78	5	3 8	34	8	8	93

*RA = Right atrium
†LVEDP = left ventricular end diastolic pressure

index and left ventricular end diastolic pressure recorded at rest and following supine leg exercise for three minutes Left ventriculography was performed in the right anterior oblique position and the left ventricle was evaluated by inspection for cavity size disorders of contractility and the presence of mitral regurgitation Selective coronary arteriography was carried out using meglumine diatrizoate (Renografin 60) Cinearteriography was recorded at 60 frames per second in the right anterior oblique left anterior oblique and postero anterior projections before and after the administration of sublingual Isordil The venous phase following coronary artery opacification was recorded by cinearteriogram in two instances

Results

All 6 patients had abnormal resting ECG s Two patients had evidence of septal fibrosis on their resting tracings manifested by poor progression of the R wave from V_1 through V_4 One subject had diffuse ischemic changes and QS complexes in Leads III and aV$_F$ suggestive of an inferior myocardial infarction The remaining 3 subjects had diffuse ST and T wave changes compatible with myocardial ischemia Three patients out of the 6 had a positive exercise tolerance test (Fig 1)

Cardiovascular hemodynamic data are summarized in Table I All 6 subjects had normal right atrial pressures The cardiac index was slightly decreased in Cases 1 and 3 and was normal in the others Case 3 had



Fig 2 A B and C Right coronary arteriograms A frame 1 B frame 7 C frame 8 Note the strikingly slow flow velocity of dye between frame 1 and frame 8

a slightly elevated resting left ventricular end diastolic pressure (normal 12) which did not change following supine leg exercise Cases 1 and 4 displayed mild and moderate rise following leg exercise, respectively

The left ventriculogram in Cases 2 and 3 displayed moderate dilatation and dyskinesia In Case 5 the left ventricle was of normal size however myocardial contractility appeared to be somewhat impaired The left ventricular angiogram was normal in the other subjects

Coronary arteriograms

Optimal quality in selective coronary arteriography was obtained The coronary arterial tree was of normal caliber in all 6 subjects There were no luminal irregularities throughout the major and secondary branches However the flow of dye in the visualized vessels featured a strikingly slow flow velocity resulting in marked delay in the clearance of the contrast medium from the coronary arterial tree (Figs 2, 3 4 and 5) The use of sublingual Isosorbide Dinitrate did not affect the caliber of the vessels or the velocity of flow The slow flow velocity was consistently reproducible in different projections and was not altered by repositioning the tip of the catheter Monitoring of cardiac rate and central aortic pressure during coronary arteriography did not reveal any significant decrease in heart rate, fall in arterial pressure, or increased duration of systolic myocardial contraction These are important considerations since an alteration in any of these factors could lead to a decrease in the velocity of flow along the coronary arterial tree

Discussion

Perfusion deficit of the myocardium regardless of the cause remains the underlying mechanism of the anginal syndrome The regulation of coronary blood flow is under the influence of several physiological factors which can be schematically divided into remote versus local factors

Remote regulation of coronary blood flow Both alpha and beta receptors are present in the small vessels of the myocardium In the presence of an ischemic myocardium there is an over all beta stimulation and vasodilatation Cholinergic stimulation also seems to induce coronary vasodilatation Coronary blood flow is intimately related to the available oxygen per liter of blood flow Arterial anoxemia increases coronary blood flow tending to keep tissue Po_2 constant The pH on the other hand exerts some effect on the hemoglobin oxygen dissociation curve an acid pH leading to a shift of the curve to the right

Local factors Myocardial perfusion is a direct function of the pressure head at the coronary ostium and is an inverse function of the arteriolar and capillary resistance[4] However due to the fact that coronary circulation occurs mainly in diastole, the diastolic phase of the cardiac cycle and the diastolic component of the blood pressure play a primary role in coronary circulation In our present series the central aortic diastolic pressure was adequate in all subjects and could not account for the slow flow velocity during selective coronary arteriography

Myocardial tissue pressure—i e the extravascular component of coronary resistance increases from epicardium to endo



Fig 3 A and B Coronary arteriograms A frame 1 Right coronary artery smooth vessel B frame 10 Segmental holdup of dye at mid level and terminally

cardium exceeding intermittently the intraventricular pressure[5] and leading to a nonhomogenous myocardial perfusion Carson and Lazzara[6] noted a decrease in myocardial contractility resulting in a marked increase in coronary blood flow during coronary arteriography in dogs which leads us to speculate that the slow flow velocity of dye noted in our subjects was not the result of the direct intracoronary injection of the contrast medium

Intravascular resistance

Coronary arteriosclerosis remains the major cause of the anginal syndrome The mechanically obstructed coronary artery fails in the absence of collaterals to deliver adequate blood supply distally thus resulting in myocardial perfusion deficit and angina Granted that selective coronary arteriography tends to underestimate luminal irregularities it is highly unlikely with our present technique[8] that significant luminal disease would be missed when interpreting the cinearteriographic results In our present study all coronary vessels down to a caliber of 1 mm were interpreted as normal by two observers

Another important cause of transient coronary luminal narrowing and slow flow of dye is a functional spasm of the coronary artery under study[9] Typical anginal attacks that have been precipitated during selective coronary arteriography by a marked and localized coronary artery spasm have responded dramatically to coronary vasodilators In our present



Fig 4 Coronary arteriogram Residual dye coating the conus branch and the terminal right main trunk

study no functional spasm was demonstrated at any time during the procedure that would account for the slow flow velocity of the dye Nevertheless all patients were given sublingual coronary vasodilators to see if the velocity of flow would be significantly affected Small vessel resistance remains the most important and yet the most controversial factor involved in regulating regional myocardial perfusion Small variations in the luminal diameter of these vessels lead to profound alterations in myocardial blood flow

There is little doubt that small vessel pathology is quite common in such disorders as collagen diseases amyloidosis idiopathic myocardiopathies diabetes mellitus certain hypersensitivity states and hematologic disorders However we are still in the speculative stage when dealing with small



Fig. 5. *A* and *B*. Coronary arteriograms. *A*, frame 1. Right coronary artery with severe segmental obstructive disease. *B*, frame 10. Note the rapid clearance of dye through the obstructed segment.

vessel pathology in arteriosclerotic heart disease[10,11] and in the anginal syndrome with grossly normal coronary arteries.

It is universally accepted that an imbalance between oxygen supply and demand leads to the myocardial hypoxia which is the underlying pathology for angina pectoris. In our 6 subjects there was no cinearteriographic evidence of coronary arteriosclerosis. On the other hand, physical and hemodynamic findings did not reveal any significant disturbances in the oxygen carrying capacity of blood such as anemia, *chronic obstructive lung disease*, or cardiac decompensation with peripheral venous hypertension and stasis.

In the present study we are therefore led to assume that the slow velocity of dye noted during selective coronary arteriography was somehow related to an abnormal *increase in small vessel resistance resulting* in restricted oxygen delivery. Physiochemical alterations in situ or localized hypersensitivity reaction brought about by the direct contact of dye with the intima remain a possibility.

A decrease in the number of perforators and in straight and narrowed major coronary vessels have been observed in angiograms of patients with obscure myocardiopathies.[12] Disorderly medial proliferation of small vessels and lesions similar to medial necrosis have been found in one of these patients. It was suggested that perhaps the arteriolar histological alterations precede those of the myocardium. Although a similarity in arteriographic findings is lacking, the same conclusions may perhaps apply to our 6 subjects, 2 of whom displayed dilated and hypocontractile left ventricles on their angiograms. These findings may reflect the early changes of myocardial dysfunction seen in cardiomyopathies. Needless to say, myocardial biopsy would have been of the utmost importance in defining the histological structure of the myocardium.

Summary

The coronary arteriograms of 6 patients with the anginal syndrome revealed a normal coronary arterial tree. This finding was associated with a strikingly slow flow rate of the angiographic dye through the major vessels. This feature is discussed in detail and a theory of small vessel disease is suggested. The purpose of this paper is to bring into focus a new angiographic finding. Its cause is hypothesized and requires clarification by further studies which should include accurate flow measurements, metabolic determinations, and myocardial biopsies.

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The relation between the conductivity of the blood and the body tissue and the amplitude of the QRS during heart filling and pericardial compression in the cat

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The QRS amplitude in poikilotherms[1] and in homeotherms[5] changes during bleeding or filling of the heart. Studies dealing with the significance of the amplitude changes of the QRS began in 1910.[1] The changes were confined to the conductivity of the fluid inside[3,6,8] and outside[9] the heart and of the immediate surrounding tissues.[9,10]

In a previous investigation[11] it was shown that the decreased amplitude of the QRS waves during filling of the turtle heart is not connected with changes of the short circuit inside the heart caused by the blood.

The aim of this work is to examine if the changes of the QRS in mammals occurring during changes in filling of the heart are a function of conductivity inside and outside the heart. Changes in heart filling can be achieved in experimental animals by direct and indirect means: (1) In a direct way, by taking out blood from the circulation[4] or pumping in an extra amount of liquids; (2) in an indirect way, by compression of the heart with the help of liquids introduced into the pericardial sac. This compression reduces the heart filling. The influence of short circuits caused by the conductivity of the blood on the QRS amplitude can be examined by filling the heart or the pericardial sac with solutions of known but different conductivity. The solutions used in our experiments were saline—isotonic NaCl solution with a conductivity similar to that of blood and body tissue, isotonic glucose solution 5 per cent, and olive oil, both of a very low conductivity.

Methods

The experiments were carried out in adult male and female cats. Anesthesia was induced by 30 mg. per kilogram of body weight of intraperitoneal sodium thiopentone. Cannulas were introduced into the trachea, femoral artery, and femoral vein

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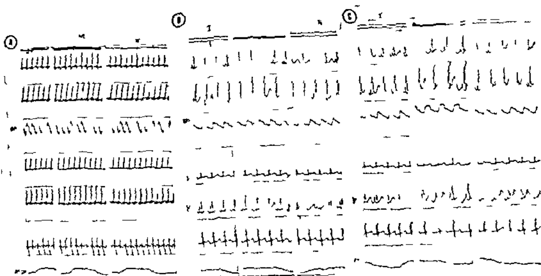


Fig. 1 ECG recording from cat before intraventricular filling (*I*), during the filling (*II*) and after return to the normal (*III*) with saline, oil and glucose. Lead I, II, III, X, Y and Z are shown. B.P. = Blood pressure. *Resp* = Respiration.

Heart catheters (gauge 10) were introduced into the left ventricle through the carotid artery for the purpose of additional filling of the ventricle with 1 to 10 ml. of either isotonic saline, isotonic glucose solution or olive oil. Overfilling of the heart during normal circulation was achieved by injection of one of these fluids into the left ventricle at the rate of 0.5 to 1 ml. per second. With each systole an increased volume (blood plus injected solution) was thrown out into the circulation. At the cessation of the injection the overfilling was stopped and heart filling thereby returned to normal. The state of overfilling therefore existed during the period of intraventricular injection of liquid. Recordings of the ECG were obtained before the overfilling, during the overfilling and after the cessation of the overfilling.

In some animals the injected olive oil produced immediate coronary artery emboli already present during overfilling. It was possible, however, to carry out experiments in which no heart emboli occurred and the electrocardiogram continued to be normal for prolonged periods. The results taken into account refer to those experiments only in which the ECG's before and after overfilling were similar.

The experiments with pericardial compression were carried out in cats artificially respirated by a Howard Respiratory pump (model 670). The rib cage was cut next to the sternum and separated with a retractor. The intact pericardium was fixed to the side of the open chest by silk sutures and a cannula was introduced into the pericardial sac for the purpose of filling. At the end of the experiment the fluid was removed from the pericardial sac through the same cannula. Control experiments were carried out in cats under the same conditions but with open pericardium. The upper side of the fixed pericardium was cut. The heart was lying in the open pericardial sac as in a bath. The intact pericardial sac as well as the open one was filled with either saline or olive oil.

Standard ECG Leads I, II, III, C_{1}, and CR_{1}, as well as the scalar tracings X, Y and Z were recorded in all experiments using a Grass model 7 six channel polygraph.

Results

Fig. 1 shows the changes in QRS amplitude recorded in cats before overfilling of the heart (part I), during the overfilling (part II) and after return to normal (part III). The figure clearly shows that the QRS amplitude increases in all the filling experiments regardless whether saline solution, *glucose* or *olive oil* were used. The increase

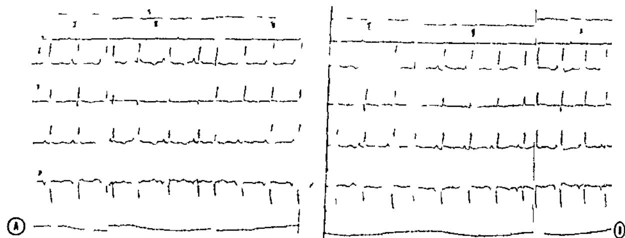


Fig. 2. ECG recording from cat before the filling of the pericardial sac (*I*), during the filling (*II*) with saline or oil, and after the removal of the fluid (*III*). Abbreviations as in Fig. 1.

was recorded in all the standard leads as well as in the scalar tracings X, Y, and Z.

Fig. 2 shows the changes in the QRS amplitude recorded before filling of the pericardial sac (part I), during filling (part II), and after removal of the fluid (part III). Filling of the pericardial sac produced compression of the heart, reduced filling, increased venous pressure, and decreased arterial pressure. In Fig. 2 it was clearly shown that even under compression with olive oil the amplitude of the QRS complex changes as in the case with saline. In both cases the amplitude of QRS was reduced during compression of the heart (part II) and returned to its original amplitude when the fluid was removed (part III).

In the control experiments (Fig. 3) when the open pericardial sac was filled with saline or with olive oil, compression on the heart did not occur. In these experiments there were no significant changes in the QRS amplitude during filling with saline and no changes at all with olive oil when compared with the amplitude before filling.

Discussion

The turtle heart reacts to bleeding with an increase of the QRS amplitude,[6] while refilling immediately produces the reverse effect.[1] According to Krasno and associates[6] influence of bleeding can be explained by the reduction of shunting circuits inside the empty heart. The mammalian heart reacts to bleeding with a decrease of the QRS

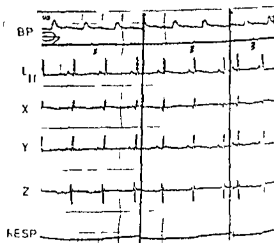


Fig. 3. ECG recording from cat before the filling of the open pericardial sac (*I*), during the filling with saline (*II*), or with oil (*III*).

amplitude,[4] a phenomenon reversed by refilling the heart with blood or saline. Overfilling causes an increase of the QRS amplitude.[4] These reactions have also been ascribed to the changes in the conductivity of intracardiac blood.[3]

If the effect of bleeding on the QRS amplitude were dependent only on the conductivity of the intracardiac fluid, one would expect the turtle and the cat to react in an identical way to bleeding and not in an opposite manner as in this case. The experimental evidences brought in the previous[11] and present work show that the different specific conductivity of substances used had no influence on the changes of the QRS amplitude during overfilling—all of them (saline and glucose solution as well as olive oil) produced the same reaction

Ishikawa and co workers[1] showed that during heart failure the QRS amplitude is decreased although the heart size is increased They showed that following clinical improvements the QRS amplitude increased accompanied by decrease in cardiac volume The fact that overfilling of healthy heart in cats (with either blood saline glucose or olive oil) causes the same increasing in the QRS amplitude as is observed during clinical improvement of heart failure shows that the short circuit effect of the increased intracavitary blood mass [1] cannot explain the changes in the QRS amplitude we are dealing with Therefore conductivity cannot be the main cause

In our previous investigations[4 11 13] the alterations of the QRS amplitude caused by bleeding were related to the changes in the filling of the normal heart i e changes in stretching of the heart and not heart size itself which have different meanings in the healthy heart or in heart failure

The dissimilarities between the reactions in turtles and cats are related to phylogenetic differences[13]

In pericarditis where the pericardial sac is filled with good conducting fluids the reduction of QRS amplitude is known This phenomenon has been explained by the short circuits outside the heart[9] The evidence in this work proves that conductivity of infused fluids (either saline or olive oil) has no influence on the decrease in the QRS amplitude Moreover the fact that filling the open pericardial sac with olive oil did *not* change the QRS amplitude while filling the intact pericardial sac did underlines the independence of this phenomenon on the conductivity The changes in QRS amplitude caused in pericardial effusion therefore may also be explained by the decreased heart filling caused by the cardial compression

With regard to the initial question whether a relation exists between the conductivity of blood and body tissue and the QRS amplitude we conclude that the conductivity of the fluids inside and outside the heart has no influence on the alteration of QRS during bleeding pericardial effusion and overfilling of the ventricle They originate from the changes in the state of filling of the normal heart—stretching the healthy heart

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Interrupted eccentric longitudinal muscle fibers of the kidney and adrenal veins

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The walls of the small veins, in general, like those of the corresponding arteries consist of three tunics. The intima is composed of the endothelium and a poorly defined internal elastic membrane. The adventitia is usually the thickest coat and it is formed by collagenic connective tissue. The media is much thinner than that of the companion artery and it consists chiefly of circularly arranged smooth muscle fibers. In some veins the inner muscle fibers of the media have a longitudinal course. The veins of certain organs, such as the maternal placenta, nail bed, retina, bone, brain, and meninges, are devoid of muscle fibers. In contrast, veins of the pregnant uterus, umbilical cord, and adrenal glands are rich in muscle fibers. In the adrenal glands of man, both the main and medullary veins show a weak development of circular muscle and extremely thick longitudinal musculature.[1]

In 1906 Furgeson noted that large longitudinal ridges of smooth muscle in the walls of the veins of the adrenal glands are constantly present in human subjects, less highly developed in the suprarenal vessels of the lower mammals, and may to some extent serve the purpose of the valves.

In 1928 Goldzieher and Sherman[3] pointed out the association of hypertrophy of the longitudinal musculature of the suprarenal veins and hypertension. In 1937 Frankl[4] described the presence of a thin circular and an extremely thick longitudinal muscle layer in the walls of the veins of the adrenal glands of adult man. He also indicated that the adrenal veins of the ox and other mammals do not show such a muscular development. In 1944 Goldzieher[5] pointed out that the adrenal veins are characterized by a singular feature, the unique development of longitudinal muscle bundles in the wall of the larger veins. He also postulated that muscle bundles act as regulators not only of the venous flow but also of the adrenal secretion. Symington[6] in 1962 contended that muscle bundles of the adrenal veins are concentric in the midportion of the gland but change into eccentric bundles at the periphery. Contraction of the eccentric muscle bundles will obstruct the blood flow from the cortical capillaries into the central vein without interfering with the blood flow in the main vein. The longitudinal muscle in the central vein accordingly has a valvelike action and controls the flow of the blood from the adrenal

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Table I. Interrupted eccentric longitudinal muscle fibers of human kidney and adrenal veins

Groups	Age		Kidney				Adrenal			
	Average	Range	FM/No. sections		F	M	FM/No. sections		F	M
1 Newborn	10 days	1-60 days	0/170	0 %	—	—	0/18?	0 %	—	—
2 Infant	8 mo	2-24 mo	0/160	0 %	—	—	0/156	0	—	—
3 Children	6 yr	2-15 yr	8/16?	5 %	2+	1+	24/96	23	2+	1+
4 Young adult	23 yr	16-30 yr	88/265	33 %	3+	1+	84/140	43 %	3+	1+
5 Mature	38 yr	31-45 yr	50/204	25 %	3+	1+	96/140	65	3+	1+
6 Middle age	53 yr	46-60 yr	31/150	20 %	3+	1+	107/134	75 %	3+	1+
7 Aged	69 yr	61-91 yr	9?/230	40 %	3+	1+	87/130	40	3+	1+

F = Fibrous. M = muscle.
*Ten cases in each group.

Table II. Interrupted eccentric longitudinal muscle fibers of rat kidney and adrenal veins

Group (No.)	Body weight		Daily treatment DHT	Kidneys			Adrenals		
	Initial	Final		No. sections	F	M	No. sections	F	M
1 (12)	50	65	—	90	1+	0	160	0	0
2 (10)	150	165	—	120	1+	0	60	0	0
3 (12)	380	380	—	80	1+	0	120	0	0
4 (10)	210	190	1 wk	75	1+	0	8[illegible]	0	0
5 (10)	210	200	2 wk	75	1+	0	80	0	0
6 (10)	210	200	3 wk	60	1+	0	40	0	0
7 (10)	220	180	4 wk	75	1+	0	58	0	0

N = number. DHT = dihydrotachysterol. F = fibrous tissue. M = longitudinal muscle bundles.
Retired breeders.

cortex. In 1967, Pavan and Gilbert[7] described the hypertrophy and fibrosis of the longitudinal muscle fibers as "micronodular phlebosclerosis," suggesting an association with age and stress. Such nodules were also found in the wall of the small veins of the kidneys.

The aim of the present study was to determine the age at which these muscle fibers are noted first in human subjects, the frequency of the fibrous and muscular fibers in various age groups, the amount of muscle versus fibrous tissue, the morphology of the fibers, and finally the presence or absence of the fibers in the sections of the adrenal glands and kidneys of rats.

Materials and methods

An arbitrary age group arrangement was made as follows: newborn, 1 to 60 days; infants, 2 to 24 months; children, 2 to 15 years; young adults, 16 to 30 years; mature adults, 31 to 45 years; middle age, 46 to 60 years; and aged, 61 years and over. Among the autopsies of several years, 10 consecutive cases were picked out for each age group with fresh tissue of the kidneys and adrenals available. Multiple sections were prepared with an attempt to examine all parts of the organs including the hilum and the periphery. Half of the sections were stained by hematoxylin and eosin and the other half by Gomori's trichrome method to differentiate between fibrous tissue and muscle fibers. Presence or absence of the fibrous or muscle bundles was graded as absent (0), minimal (1+), moderate (2+), and large amount (3+). An average was calculated for each group as indicated in Table I. The number of the sections prepared of human kidneys and adrenals was 2,319. History, physical findings, blood

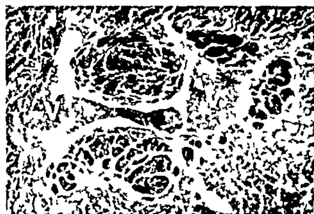


Fig. 1. Interrupted eccentric longitudinal muscle fibers are noted in the wall of a vein (V) in the central part of the adrenal gland. Severe hypertrophy of a muscle bundle is seen in the upper part of the photograph causing partial occlusion of the lumen of the vein. (Gomori's trichrome. ×40.)

pressure, diagnosis, and autopsy findings were noted in each case.

In the animal experimentation part of the study, 74 female Sprague-Dawley rats of various weights were divided into 12 groups as indicated in Table II. The animals were subdivided into groups of 3 to 5. They were kept in suspended metal cages and had free access to water and Purina Laboratory Chow. The animal quarters were air conditioned and the temperature was kept around 75° F. at all times. Some of the groups were treated by dihydrotachysterol (DHT) at the dose of 50 μg in 0.5 c.c. of corn oil given by mouth daily.[8] This was done to produce progeria-like syndrome and severe arteriosclerosis in a short period of time.[9] The length of the DHT treatment varied among the groups from 1 to 4 weeks as indicated in Table II. At the end of the experiments, all animals were put to death by ether; the kidneys and adrenals were removed and fixed in Bouin's solution for 48 hours after which they were sectioned and processed for microscopic examination. The total number of slides prepared from rat kidneys and adrenals was 1,173. Half of the slides were stained by hematoxylin and eosin; the rest by the trichrome technique for observation of the muscle fibers.

Results

The longitudinal muscle fibers along the course of the small veins were found not only in the adrenals but also in the human



Fig. 2. Eccentric muscle bundles are noted in the wall of a small vein outside and adjacent to the adrenal gland. (Trichrome stain. ×40.)

kidney sections. A large amount of fibrous tissue is noted surrounding the neurovascular complex entering the hilum of the kidney. This is true both for human as well as rat kidneys. Longitudinal muscle fibers, however, are completely absent in the sections of the kidneys and adrenals of the rats. The connective tissue present at the hilum of the kidneys extends into the parenchyma along with the blood vessels. Longitudinal muscle fibers are noted in the wall of the veins in the hilum of the kidneys as well as in the parenchyma. The amount and the frequency of their presence, however, reduce as the neurovascular complex travels deeper into the parenchyma. They are seen occasionally in the subcapsular region of the kidneys. Occasional veins outside of the adrenal in the adipose tissue surrounding the gland were found demonstrating the eccentric longitudinal muscle fibers.

Several adrenal glands not indicated in the table were semiserially sectioned



Fig. 3. Higher magnification of Fig. 2 disclosing the detail of the structure of the myomatous nodule and the wall of the vein. (Trichrome ×700.)



Fig. 5. The neurovascular complex deeper in the parenchyma of the kidney shown; collection of the eccentric longitudinal muscle fiber adjacent to the vein. (Trichrome ×40.)



Fig. 4. The neurovascular complex in the parenchyma of the kidney. Note the artery on top (A), two large nerve bundles (*N*) below the artery with a few *small* veins on the left side of the photograph. Longitudinal muscle bundles (darker in color) are noted in the lower part of the picture. Fibrosis and hyalinization (*H*) are also noted. (Trichrome ×40.)

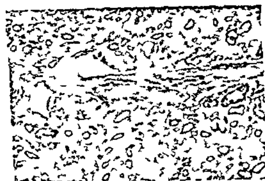


Fig. 6. Arrangement of the longitudinal muscle fibers near the veins is indicated in this photograph *deep in the* parenchyma of the kidney. (Hematoxylin and eosin ×40.)

numbered in sequence and processed for microscopic examination, they disclosed no regular parallel or *spiral* pattern for eccentric longitudinal muscle fibers. It appears that these muscle fibers are interrupted and patchy rather than continuous.

In the animal experiment part of the study (Table II), the rats of various age groups as well as those made arteriosclerotic and progeric by Selye's dihydrotachysterol method showed no evidence of longitudinal muscle fibers which *could be* identified by light microscopy in either the adrenal or kidney. Fibrous tissue, *however*, is present near the hilum of the kidney surrounding the neurovascular *complex entering* the organ.

No association was found between the high blood pressure and the presence of hypertrophic longitudinal muscle fibers of the adrenals and kidneys.

Discussion

Concentric longitudinal muscle fibers are present in the wall of many veins including the *renal* veins. Aside from these, in the neurovascular complex entering the hilum of the kidneys, many longitudinal muscle fibers are noted which are irregularly distributed. Most of them, however, *are near* or adjacent to the smaller veins which have thin walls. Extension of these muscle fibers into the parenchyma of the kidney is noted along with the branching of the neurovascular complex. Deeper *in the* parenchyma where isolated small veins are noted, fairly frequently one recognizes the presence of interrupted eccentric longitudinal muscle



Fig 7 Marked hypertrophy of the muscle fibers is noted in the wall of a vein near the periphery of the kidney (Trichrome ×200)



Fig 9 Higher magnification of Fig 8 discloses the finer structure of the muscle bundle and the wall of the vein (Trichrome ×200)



Fig 8 An almost collapsed vein is noted (V) near the top of the photograph with bundles of hypertrophic longitudinal muscle fibers adjacent to it Some of the muscle fibers extend to a second vein (V) on the right upper corner of the picture (Trichrome ×40)



Fig 10 A small vein is noted in the left upper corner of the photograph with three groups of eccentric longitudinal muscle fibers one of which is protruding into the lumen (Trichrome ×40)

fibers adjacent to the wall of the veins but they are not seen near the arteries or elsewhere In occasional sections some of the fibers of the longitudinal musculature are noted extending from one small vein to the next The muscle fibers are noted infrequently at the periphery of the kidney parenchyma, but always adjacent to a small vein The function of these fibers in the kidney is not known

The presence of the longitudinal muscle fibers along the course of the central adrenal veins has been known for some time [1] It should be noted however that these eccentric muscle bundles both in the adrenal and kidney are not continuous but interrupted and patchy They are also found not only in the medulla of the adrenal but occasionally in the adipose tissue adjacent to the gland

In regard to the function of these muscle fibers it has been postulated by some that they control the blood flow and the hormonal output of the adrenal [5] Others have suggested that they function as a valve [6] We feel that the latter hypothesis is more plausible since the fibers are interrupted

It has been said that the longitudinal muscle fibers are present in the adrenal of adult humans [4] Following our study we feel that it is more precise to say that such longitudinal muscle fibers do not exist at the time of birth and they are not seen in infants They are, however present in children but not as frequently as they are seen in adults

Ox and other mammals have been said not to show eccentric longitudinal muscular development in the veins of the adrenal [4] Another study suggests that such muscle



Fi 11 The same vein as in Fig 10 is demonstrated in the right upper corner of the photograph with detailed structures of the vein and the muscle fibers (Trichrome X200)

fibers in the suprarenal glands are less developed in mammals other than man[4] In our study of the adrenals and kidneys of rats we did not find any eccentric longitudinal muscle fibers regardless of the age of the animals

Association of the hypertrophy of the longitudinal muscle fibers in the central adrenal veins with hypertension was noted by Goldzieher and Sherman[3] Such a relationship however has not been confirmed by this or any other study as far as we know The muscle fibers are not present in the newborns and infants They appear during the childhood and increase in number gradually in later life Therefore their development could be related to sex hormones and maturity Nodular hypertrophy and particularly fibrosis of these muscle bundles in later life has been called micronodular phlebosclerosis[7] We prefer to assume that such a process could be related to age and stress[7] rather than a specific disease entity such as hypertension[3]

Summary

A large number of sections were taken from adrenals and kidneys of human subjects of various age groups The sections were stained by hematoxylin and trichrome methods and they were examined for presence or absence of interrupted eccentric longitudinal muscle fibers along the course of the veins It is noted that these muscle fibers are absent in newborns and infants they are present in small amounts in children and they increase with age The fibrous tissue particularly is noted to increase as age advances These are more easily found in the adrenals than they are in the kidneys In older people focal hypertrophy and fibrosis of these muscle bundles could form a nodular pattern occluding the lumen of the veins It appears to us that hypertrophy and fibrosis of these muscle fibers are related to old age and stress rather than to a particular disease process such as hypertension Examination of the adrenals and kidneys of rats showed no evidence of longitudinal muscle fibers

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Fig 7 Marked hypertrophy of the muscle fibers is noted in the wall of a vein near the periphery of the kidney (Trichrome ×200)


Fig 9 Higher magnification of Fig 8 disclosing the finer structures of the muscle bundle and the wall of the vein (Trichrome ×200)


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sixth intercostal space The ends of the nylon snare were passed through the tube the flared end of which was sutured to the pericardium (Fig 1) The tube was then filled with petroleum jelly to form an air seal The pericardium was sutured and the implanted probe wires and left atrial catheter were brought through the chest at the posterior end of the incision and the thorax was closed During surgery a slow continuous intravenous drip of 5 per cent dextrose in water was maintained and whole blood from donor rhesus monkeys was transfused according to the blood loss Mephentermine sulfate (mg) (Wyamine—Wyeth Laboratories Inc) was given intravenously if the blood pressure dropped below normal levels especially after dissection around the aorta and placement of the flow probe After surgery 1 200 000 units of benzathine penicillin and procaine penicillin G (Bicillin CR—Wyeth Laboratories Inc) were given intramuscularly the monkey was then placed in a specially designed suit to recuperate in a cage for 3 to 5 days

On the morning of occlusion the animal was placed in a restraining chair and electrocardiographic (ECG) electrodes were sutured to the proximal part of the four limbs and to three chest positions (V_1 and V_2 were 1 cm below the right and left mammary papilla respectively V_5 was placed 1 cm lower than V_2 and at the *anterior axillary line*) *Blood* pressure transducers were placed at the level of the heart and 4 to 6 recordings at 15 minute intervals were averaged for the control values After a steady state had been reached the snare was gradually tightened over a period of 1 to 2 minutes while the ECG was constantly monitored on a 6 channel oscilloscopic recorder (Sanborn Model 350) Tension on the snare with counterpressure on the tubing produced complete occlusion of the artery The expected end point was indicated by an injury current (S T segment elevation) in any of the precordial leads At appropriate intervals the following parameters were recorded (1) 9 leads ECG (2) blood flow in the ascending aorta (considered to represent cardiac output when coronary flow is disregarded) (3) left atrial pressure (4) aortic systolic diastolic mean and pulse pressure and (5) heart rate

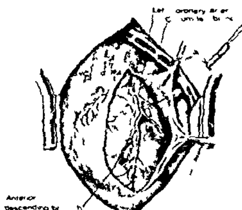


Fig 1 Drawing of midline sternotomy exposing pericardial cavity and illustrating the location of the snare used to produce myocardial infarction *SVC* = superior vena cava *Ao* = aorta *PA* = pulmonary artery

After infarction recordings were taken at 5 minute intervals for 1/2 hour 10 minute intervals for 1 hour 30 minute intervals for 2½ hours and 1 hour intervals thereafter during each working day The monkeys were continuously observed until 5 P M and recordings were taken of any significant changes The animals were then periodically observed until midnight but no recordings were made after 5 P M External defibrillation with d c current countershock (American Optical Co) at 200 watt seconds was applied if serious ventricular arrhythmias (ventricular tachycardia flutter or fibrillation) were present When the animals died or when the experiments were terminated 24 to 98 hours after infarction necropsies were performed to verify the position of the snare and the size *and location* of the infarction

For prediction of clinical outcome we used discriminant analysis[19] based on the general formula

$$L = K + aW + bX + cY + dZ$$

where L = discriminant function K = constant a = coefficient for aortic systolic *blood* pressure W b = coefficient for aortic diastolic blood pressure X c = coefficient for aortic mean blood pressure Y and

Experimental myocardial infarction in unanesthetized monkeys*

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The literature on experimental myocardial infarction in monkeys is very limited.[1-5] Most studies in the past have used species other than nonhuman primates such as the dog[6-10] and pig.[11] Moreover, the observations were made mainly on acute preparations performed under various types of anesthetics.[1-11] Recently, several reports have described methods of producing coronary occlusion in conscious dogs.[12-18] This investigation was undertaken to study cardiovascular changes in unanesthetized monkeys from the moment myocardial infarction was induced.

Methods

The experimental animals were 12 male and 22 female adult *Macaca mulatta* weighing between 4.5 and 9.5 kilograms. Twenty mg. of succinylcholine chloride (Quelicin, Abbott) were administered intravenously and a cuffed endotracheal tube was inserted. General anesthesia, 0.5 to 1.25 per cent halothane (Fluothane, Ayerst) vaporized in a Fluotec vaporizer with 40 per cent nitrous oxide and 60 per cent oxygen, was administered with a Boyle's anesthesia machine.

A polyvinyl catheter was implanted in the aorta via the femoral artery and was connected to a transducer (Statham Model p23Db) to monitor blood pressure during surgery and during the ligation experiment several days later. After the thorax had been opened by a midline sternotomy, an electromagnetic square wave flow probe (Biotronex Laboratories) was placed around the aorta just superior to the coronary arteries. A polyvinyl catheter was placed in the left atrial appendage by means of a purse string suture. A nylon filament snare (8 lb. test nylon swaged on a needle) was passed through the pericardium and loosely placed around the left anterior descending coronary artery 2 or 3 mm. distal to the origin of the circumflex branch. By means of a stab incision, a polyvinyl tube with a flared tip was passed through the left

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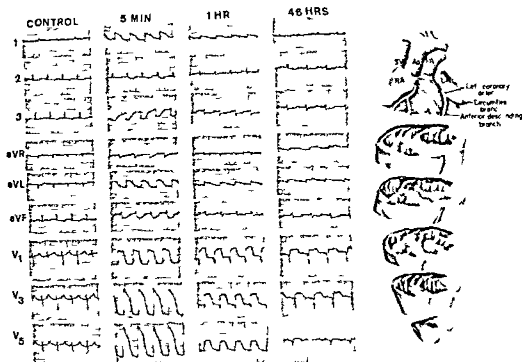


Fig. 3 Serial electrocardiograms with drawing of heart illustrating a more extensive area of infarction than in Fig. 2

Immediately after the snare was pulled the animals became agitated for 1 to 2 minutes. In general, those animals with initial decreases greater than 50 per cent in aortic blood flow and 30 per cent in mean aortic pressure appeared dazed, did not respond immediately to external stimuli, did not eat or drink, did not survive longer than 6½ hours after myocardial infarction, and presumably died from cardiogenic shock. The animals that survived the infarction more than 12 hours remained alert and responsive to their environment and ate and drank normally.

Electrocardiogram. Immediately after the obstruction of the left anterior descending coronary artery, the S-T segment became slightly elevated in Leads I, aV_L, and the precordial leads and depressed in Leads II, III, and aV_F; the rapid increase in S-T displacement became marked (several mm.) 3 to 4 minutes later (Fig. 2). About 30 minutes after ligation, a small Q wave appeared in the standard leads and in Leads aV_F and V_1 and increased in amplitude; a QS pattern developed in the precordial leads. Twenty-four hours later the S-T displacement tended to disappear in the frontal plane but remained elevated in the precordial leads. The QS pattern persisted in the animals that survived for 4 days after the occlusion procedure. This pattern corresponding to infarction of the anterior and part of the lateral wall of the left ventricle, the anterior half to two thirds of the septum, and a small portion of the anterior right ventricular wall, was determined by postmortem examinations. A slightly different ECG pattern was observed in two animals that had left ventricular necrosis extending much farther laterally than was general (Fig. 3) and in another monkey with a small and strictly lateral infarction of the left ventricular wall (Fig. 4).

Right bundle branch block (RBBB) was observed in 13 animals after snare ligation. The conduction defect apparently did not affect survival and occurred about equally in both the alive and dead groups. In most cases it was evident in the one hour recording after infarction; however, a few animals did not develop RBBB for several hours. RBBB was present in one monkey one hour after ligation but had disappeared

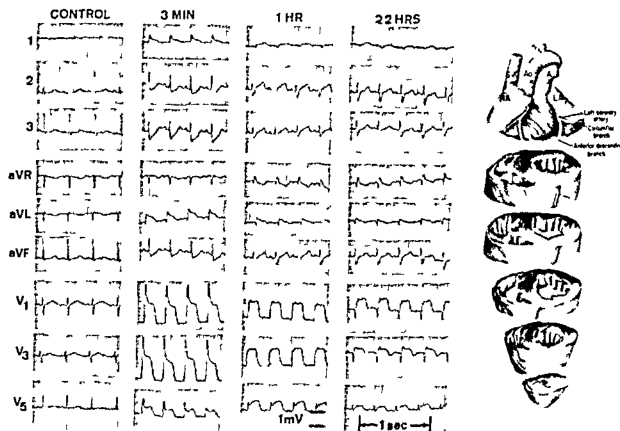


Fig 2 Serial electrocardiograms with drawing of heart illustrating pale area of infarction typically found after ligation of the left anterior descending coronary artery in the monkey In this animal right bundle branch block was also present after infarction In these and the following figures the ECG was standardized at 1 cm per millivolt and the paper speed was 50 mm per second

d = coefficient for aortic mean blood flow Z At selected periods after ligation (see *Results* below) values were obtained from all monkeys for systolic diastolic and mean blood pressure and for aortic flow With these data and a program written in Fortran II and executed on a Xerox Data System Model 920 digital computer, the constant and coefficients were determined for the "alive and 'dead groups separately The pressures and flows from individual animals were then used with the previously generated constant and coefficients from each group This produced an L_1 and L function for every individual Monkeys whose L_1 was larger than L_2 were predicted to survive retrospectively The retrospective predictions were compared with the observed events to determine the per cent of accuracy

Results

Five of the 34 animals undergoing surgery died postoperatively before ligation The 29 survivors had the snare ligated, in 3 of these the ligation was unsuccessful because misplacement of the snare excluded the coronary artery or included part of the pulmonary valve, or the snare broke The remaining 26 were divided into two groups (1) Group I ('dead) comprised the 11 monkeys that died within 6½ hours from myocardial infarction with a syndrome resembling cardiogenic shock and (2) Group II (alive) comprised the 15 monkeys that survived myocardial infarction more than 12 hours and in many cases were killed 24 to 98 hours after infarction No deaths occurred in the interval between 6½ and 12 hours after infarction Five animals that died during the night but more than 12 hours after infarction may have had cardiogenic shock however the possibility of a fatal arrhythmia cannot be ruled out Since their aortic blood flow was never under 55 per cent (percentages refer to control values taken as 100 per cent), and mean aortic pressure never was less than 70 per cent during the observed period they were placed in Group II

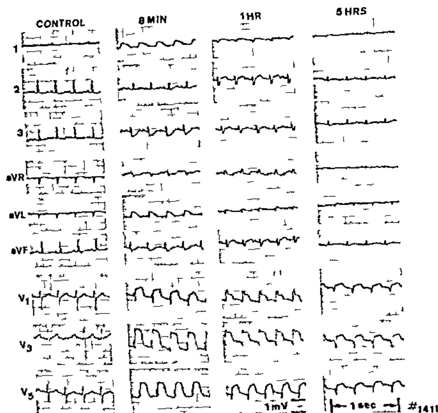


Fig. 5 After infarction transitory right bundle branch block was apparent in the one hour tracing but had disappeared by the time of the 5 hour tracing

complete A-V block with idioventricular rhythm (Fig. 7 C), the atrial rate was 215 beats per minute and the ventricular rate was 60 beats per minute. The aortic blood pressure was 95/50 mm Hg. About 1½ hours later (Fig. 7 D) the arrhythmia changed to first-degree A-V block with a P-R interval of 0.13 seconds (in a study of 351 *Macaca mulatta*[20] the P-R interval was 0.07 ± 0.01 sec.), the heart rate was 100 beats per minute, and the aortic blood pressure was 110/65 mm Hg. The monkey remained alert and ate well. When it was finally killed 98 hours after the myocardial infarction the first-degree A-V block was still present and the heart rate and blood pressure were unchanged. The possibility of second-degree A-V block was considered because a P wave could be buried in the T wave, but this could not be confirmed.

Hemodynamics. The Group I animals displayed severe hemodynamic changes immediately after coronary ligation and a partial blood pressure recovery about 1 hour after ligation (Fig. 8). They also showed wider and more frequent variations than the Group II animals. In general, the aortic flow (cardiac output minus coronary flow) dropped from the 100 per cent control value to 45 per cent shortly after coronary ligation. Although the flow fluctuated generally, it did not rise above 50 per cent of the control value throughout the survival period. Immediately after occlusion the aortic mean blood pressure fell to about 60 per cent of the control values, slowly rose in some cases to within 75 per cent of the control values about 1 hour after ligation, and then progressively declined until death.

The hemodynamic changes were less severe in Group II animals than in Group I animals. The aortic flow dropped immediately after coronary ligation to about 65 per cent of the control values but generally never below 55 per cent at any time during

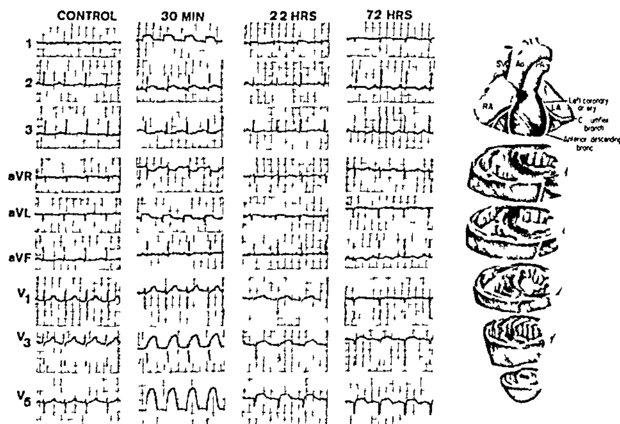


Fig. 4. Serial electrocardiograms with drawing of heart from monkey No. 19 with a lateral myocardial infarction.

by the 5 hour tracing (Fig. 5). In another animal (Fig. 6) presurgery tracings illustrated different degrees of RBBB alternately, possibly with left anterior hemiblock. After surgery but before ligation the block was incomplete and the alternation had ceased; more complete degrees of RBBB were observed in the two tracings after snare ligation.

Premature ventricular beats were common immediately after coronary occlusion but the most serious and frequent arrhythmia was ventricular fibrillation, one to 9 episodes of which occurred in 18 animals. Ventricular fibrillation was noted in 2 animals about 24 hours after ligation; the other 57 episodes were observed within 40 minutes after coronary occlusion. These arrhythmias were successfully terminated with d.c. countershocks delivered with external paddles at 200 watt-seconds. Ventricular fibrillation did not appear to affect survival, 35 episodes occurred in 11 of the 15 (73 per cent) monkeys in Group II and 24 episodes occurred in 7 of the 11 (63 per cent) animals of Group I. In two instances a recorded arrhythmia could have accounted for the death of one animal in each group.

Ventricular fibrillation and ventricular premature beats were the only arrhythmias observed during the first hours after the infarction; other complex arrhythmias were observed later on. Twenty-two and one-half hours after myocardial infarction a bigeminal rhythm in monkey No. 18 was followed shortly by spontaneous recovery to normal sinus rhythm. The aortic blood pressure during the arrhythmia was about 80/35 mm. Hg, which rose to 120/80 when the arrhythmia converted. Serious arrhythmias also occurred in the animal kept alive the longest. About 25 hours after coronary ligation either ventricular tachycardia or flutter at a rate of 430 to 500 beats per minute was observed in monkey No. 17 (Fig. 7, A); the aortic mean blood pressure fell to about 50 mm. Hg. This arrhythmia was quickly followed by ventricular fibrillation which was successfully defibrillated by d.c. countershock; after defibrillation the aortic blood pressure was 110/65 mm. Hg (Fig. 7, B). Forty-six hours after myocardial infarction this animal had

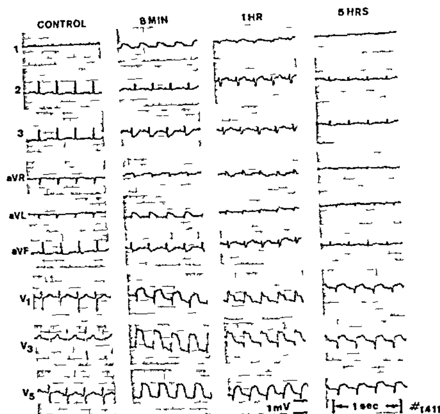


Fig 5 After infarction transitory right bundle branch block was apparent in the one hour tracing but had disappeared by the time of the 5 hour tracing

complete A V block with idioventricular rhythm (Fig 7 C) the atrial rate was 215 beats per minute and the ventricular rate was 70 beats per minute The aortic blood pressure was 95 50 mm Hg About 1½ hours later (Fig 7 D) the arrhythmia changed to first degree A V block with a P R interval of 0 13 seconds (in a study of 351 *Macaca mulatta* [8] the P R interval was 0 07 ± 0 01 sec) the heart rate was 100 beats per minute and the aortic blood pressure was 110 65 mm Hg The monkey remained alert and ate well when it was finally killed 98 hours after the myocardial infarction the first-degree A V block was still present and the heart rate and blood pressure were unchanged The possibility of second-degree A V block was considered because a P wave could be buried in the T wave but this could not be confirmed

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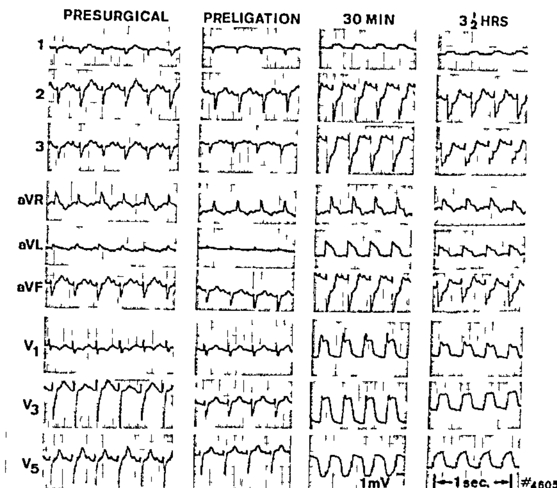


Fig 6 Presurgery tracings illustrate different degrees of right bundle branch block (RBBB) alternately After surgery but before ligation the block was incomplete and the alternation had ceased more complete degrees of RBBB were observed in the two tracings after snare ligation

the experiment Initially, the aortic mean blood pressure fell to about 75 per cent of the control values Afterwards it rose earlier and more rapidly than in Group I animals to about 80 to 85 per cent of the control values and remained relatively stable thereafter

In the early postinfarction period there was considerable overlapping between Group I and Group II animals in heart rate and in mean left atrial pressure In the later stages the mean left atrial pressure in Group II animals tended to remain elevated but showed a steady decline in Group I animals

Since systolic/diastolic and electronic mean blood pressures had been recorded during the experiments we decided to use this somewhat artificial division into three components along with the flow measurements to develop a computer program for discriminant analysis for future experiments in our laboratory We analyzed several arrangements of the data by selecting the pressure and flow measurements for each animal at certain time periods after infarction (10 15 and 30 minutes), by selecting an average value for the pressure and flow measurements from several recordings during the first 30 minutes after infarction or by selecting the data for each animal at the time of its lowest systolic diastolic mean or flow measurements during the first 30 minutes after infarction In all cases the preceding data arrangements were analyzed by expressing the blood pressure values in mm Hg and by expressing them as a percentage of the animal's own control value and by including or excluding the flow measurements The best arrangement was to select the blood pressure and flow measurements for each animal at the time of its lowest diastolic blood pressure recording during the 30 minute

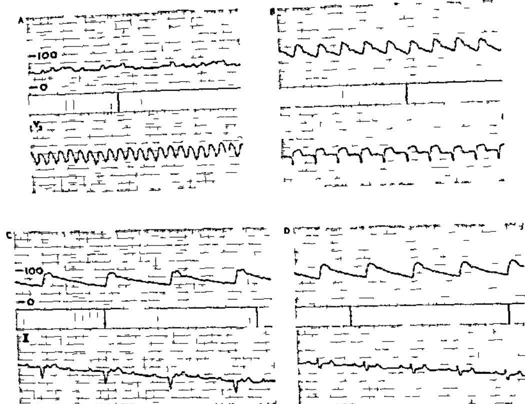


Fig 7 *A* through *D* Tracings from monkey No 17 *A* About 25 hours after coronary ligation either ventricular tachycardia or flutter at a rate of 430 to 500 beats per minute was observed The aortic mean blood pressure was about 50 mm. Hg This arrhythmia was quickly followed by ventricular fibrillation. *B* After successful defibrillation by d c countershock the aortic blood pressure was 110/65 mm Hg *C* Forty six hours after infarction complete heart block was present with an atrial rate of 215 and a ventricular rate of 70 beats per minute. The aortic blood pressure was 95/50 mm Hg *D* About 1½ hours later the arrhythmia changed to first-degree heart block with a P R interval of 0 13 seconds The heart rate was 100 beats per minute and the aortic blood pressure was 110/65 mm. Hg and remained unchanged until the animal was finally killed 98 hours after myocardial infarction

postligation period with blood pressure values expressed in mm Hg Retrospectively this data arrangement correctly predicted 100 per cent (11 out of 11) of the monkeys dying from myocardial infarction with shock and 93 per cent (14 out of 15) of the monkeys surviving for more than 12 hours Statistical analyses of the hemodynamic data used in this arrangement are given in Table I After the experimental coronary occlusion blood pressure measurements and aortic flow fell significantly ($p < 0.001$) in both groups of animals The largest decrease after infarction occurred in the aortic flow which in Group I dropped 63 per cent and in Group II fell 38 per cent The two groups did not differ significantly in their control values however after myocardial infarction they differed significantly

The other data arrangements did not predict so accurately the arrangements that included aortic blood flow were more accurate than those without it but predictions based on flow measurements alone were even less accurate Arrangements using values at a fixed time period after the infarction or each animal s average value from several recordings taken immediately after the infarction were also less accurate

Pathology A complete postmortem examination was performed on each animal After the intact heart had been fixed for several days the ligation site was dissected under the microscope for verification of

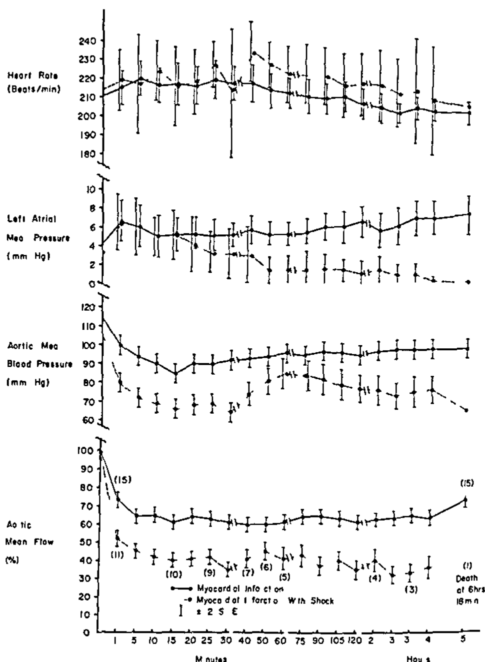


Fig. 8 Aortic blood pressure and mean flow illustrating a critical time period that occurred in the first 30 minutes after myocardial infarction followed by a partial recovery period and subsequent progressive deterioration for the cardiogenic shock group. Numbers within parentheses indicate the number of animals used for mean and standard error at that time period.

placement of the snare. Then the heart was cut in horizontal slices 3 to 5 mm thick from the apex to the A V sulcus usually 9 to 11 slices per heart. A full microscopic section was made from each paraffin embedded slice and stained with hematoxylin and eosin.

Group I. Death occurred too early for anatomical changes of infarction to be seen in these animals, although occlusion of the left anterior descending coronary artery was demonstrated. Various degrees of renal tubular necrosis were found in 5 monkeys. The histological changes ranged from patchy areas of coagulation necrosis of convoluted tubules with occasional neutrophil casts and early regeneration to wedge shaped areas of cortical necrosis in one monkey. Two of these animals also had histological evidence of anoxic paracentral necrosis in the liver and splenic infarcts. In some cases these visceral ne

Table I Comparison of hemodynamic data employed in discriminant analysis

Variables	Group I (dead)		Group II (alive)		Group I versus Group II	
	Control (Mean ± SD)	*Postligation (Mean ± SD)*	*Control (Mean ± SD)*	*Postligation (Mean ± SD)*	*Control I*	*Postligation I*
Aortic systolic b p	147 ± 12	81 ± 9†	154 ± 27	107 ± 27†	NS§	< 0 01
Aortic diastolic b p	89 ± 10	47 ± 7†	95 ± 18	65 ± 19†	NS	< 0 01
Aortic mean b p	109 ± 11	60 ± 8†	115 ± 20	81 ± 20†	NS	< 0 01
Aortic mean flow (%)	100	37 ± 6†	100	67 ± 14†	—‡	< 0 001

*b p = blood p re mm Hg
†Significa tly d ff t f om co tr l p < 0 001 p d t t t
‡C t ol l e f 100 per ce t l ll num ls.
§NS = non- g fi t no pa ed t t t

croses were clearly older than the post infarction time

Group II At about 14 hours after infarction no gross evidence of an infarct was seen Histological sections showed increased cytoplasmic eosinophilia smudging of cross striations and shrinkage of nuclei At 24 hours the infarction was characterized grossly by an area of vague pallor the histological signs were confined to cell shrinkage loss of nuclei edema and minimal marginal leukocytic infiltrate By 48 hours the infarct was grossly visible below the snare as an irregularly shaped area of gray discoloration At this time there were histological signs of massive necrosis with peripheral leukocytic infiltration A zone of neutrophils marked the boundary of the infarct by 72 hours but organization had not yet begun At 96 hours the complete central necrosis was bordered by a band of largely necrotic neutrophils and numerous zones of young granulation tissue

The distribution of necrosis in these animals was fairly constant nearly all of the apex was involved and higher sections up to the level of the ligation showed necrosis in the anterior and part of the lateral wall of the left ventricle the anterior half or two thirds of the septum and a small portion of the anterior right ventricular wall Generally a narrow zone of subendocardial muscle remained viable However in monkey No 17 the necrosis extended to the ventricular lumen and a mural thrombus was attached thrombi were found in the renal arteries presumably embolic from the heart Thrombi were not found in the anterior descending coronary artery below the point of ligation This is also the only animal that was kept alive until 98 hours after ligation other animals were usually killed 48 hours after infarction Two animals had left ventricular necrosis extending much farther laterally than was general in one monkey anomalous duplicate anterior descending coronary arteries had been included in the snare in the other monkey the artery was unusually large (Fig 3) A small and strictly lateral infarction of the left ventricular wall was found in animal No 19 (Fig 4) In this animal the snare did not include the anterior descending artery but its close proximity to the origin of the circumflex branch may have resulted in reduced blood flow caused by compression of the surrounding tissue

Various degrees of renal tubular necrosis were found in 5 monkeys 3 of which also had evidence of anoxic paracentral necrosis of the liver Renal infarcts were found in 6 animals 2 of which also had necrosis of the zona reticularis of the adrenal gland The one case of hepatic vein thrombosis was of unknown origin Again in some cases these lesions were clearly older than the postinfarction time

Discussion

Reports of spontaneous myocardial infarction are rare in nonhuman primates[1-4] and the literature on experimental myocardial infarction in them is also very limited[1,5] The most extensive use of non

hum in primates was made by de Waart and co workers[3] who described ECG changes after ligation of either the left anterior descending or the right coronary artery in 31 animals (*Macaca irus*). The present study contributes electrocardiographic and hemodynamic data in unanesthetized, chair restrained rhesus monkeys.

Many different methods have been used to induce experimental myocardial infarction in several species including variations of snare devices in open chest[1] or closed chest animals[16,17] and snares occluded by remote radio control.[5] Coronary artery occlusion has been achieved by thrombus formation after direct electrical current applied to an electrode catheter[6,8,12] and by balloon cuffs[11,18] or Ameroid constrictors.[29] Other methods have produced coronary artery obstruction by embolism.[7,10,13,14] In man, 70 per cent of coronary artery occlusions occur within 3 to 4 cm. of the coronary ostia.[33] In our study, the snare of nylon swaged on a needle causes little trauma to the heart and allows direct visualization and placement on the proximal region of the coronary artery. Although this method does require preparative surgery, it does not need fluoroscopic equipment nor the use of anesthetics on the day of ligation. Most of the closed chest methods require some surgical manipulation under anesthesia immediately before creation of the infarction. The anesthetic agent itself may have a direct depressant effect on the myocardium and may produce marked changes in the cardiovascular system[30] or it may modify neurohumoral mechanisms that determine circulatory system responses to severe myocardial trauma.[31,3]

Because of the tractable nature and ease of training dogs, studies with continuous monitoring devices are possible in these animals without anesthesia or restraining devices.[16,18] Unfortunately, in most studies aggressiveness and the difficulty of training nonhuman primates make it necessary to use some type of plastic restraining chair as we did. However, this partial restriction of the animal in the sitting position may introduce hemodynamic factors not found, for instance, in man in the supine position.

Ventricular fibrillation is an early and frequently observed event after acute coronary occlusion.[8,12,1,13,31] In one study,[8] 45 out of 57 (79 per cent) dogs experienced episodes of ventricular fibrillation within the first hour after infarction. In monkeys the chance of fibrillation after ligation was found to be greatest during the first 40 minutes.[34] Although many drugs have been studied for their antiarrhythmic activity,[31] their use complicates the evaluation of experimental myocardial infarction. In dogs, ventricular fibrillation did not occur when ligation of the coronary artery was accomplished slowly in two stages[15] or when a balloon cuff was inflated slowly.[11] Multiple episodes of ventricular fibrillation in the same animal have not been reported. In our study, where an external defibrillator and continuous ECG monitoring were available, 15 of 18 monkeys experienced more than one episode of ventricular fibrillation, usually within 40 minutes after infarction; these episodes occurred about equally between the survivors and nonsurvivors. Moreover, complex arrhythmias other than ventricular fibrillation did not develop until several hours after the coronary occlusion; this has also been reported by other investigators.[15,18]

An increased heart rate has been described after experimental infarction.[16,15] Little difference occurred in our study, where the control heart rates and blood pressures were also higher than those reported in chronically chair restrained rhesus monkeys.[3] The animals probably had not reached base line values before the experiment started. Although an average of 4 preligation recordings were made during a 1 to 2 hour control period, no special precautions had been taken. Conditioning to the restraining chair and isolation might be considered useful adjuncts to the experiment.

Because death occurred too early for histological changes of myocardial infarction to be observed in Group I monkeys, no comparison of the infarcts could be made with Group II; however, the ECGs were similar. Anatomical changes in the kidney ranged from necrosis of scattered groups of tubules to wedge shaped areas of cortical necrosis. The latter may have been simple infarcts from catheter emboli that were not found, although the glomeruli were usually spared. No relationship be

tween renal tubular necrosis and blood administration during surgery was found The renal damage may have been related to hypotension during surgery especially after dissection around the aorta and placement of the flow probe In animals that survived surgery 5 days or more early tubular regeneration was frequently noted How much some degree of impairment of kidney function contributed to later deaths could not be ascertained a more detailed study of renal function would be needed More renal lesions (and the only adrenal lesions) were found in Group II (alive) monkeys than in Group I (dead) monkeys

Cardiogenic shock is a grave complication of myocardial infarction and usually carries a mortality rate of about 80 per cent in man[36,37] Although much has been written about it[38,39] precise definitions are difficult Criteria reported by some investigators[12,13] for experimental cardiogenic shock include (1) a fall in mean arterial pressure of at least 30 per cent with no recovery for at least 30 minutes (2) ECG evidence of severe ischemia with no arrhythmias to account for the fall in blood pressure and (3) initial reduction of the cardiac output by 50 per cent In Group I animals the aortic flow (cardiac output minus coronary flow) initially dropped to 45 per cent and generally did not rise above 50 per cent throughout the survival period After a marked decrease the mean aortic pressure did not rise above 75 per cent of the control value in the survival period Furthermore all these animals died within 6^1 hours after myocardial infarction and we feel that the definition of cardiogenic shock can be sustained

Retrospectively by means of discriminant analysis and based on information obtained within 30 minutes after infarction the death or survival of 25 out of the 26 animals was accurately predicted With the computer program other parameters could easily be added rather than the somewhat artificial division of blood pressure and these parameters could be used in a prospective rather than in a retrospective study A model of myocardial infarction in unanesthetized monkeys with an early prediction of death or survival may allow time for studies on the therapy of cardiogenic shock which might give some insight into this condition in man

Summary

Experiments were undertaken to study myocardial infarction in non human primates without the use of anesthetics or sedatives During surgery a snare was placed loosely around the left anterior descending coronary artery in 34 rhesus monkeys (*Macaca mulatta*) Several days later myocardial infarction was studied from the moment it was induced The technique was reproducible and the distribution of necrosis was fairly constant Aortic flow aortic blood pressure left atrial pressure and the ECG were monitored A computer program for discriminant analysis based on data obtained within 30 minutes after infarction resulted in retrospective predictions of 100 per cent in animals dying from cardiogenic shock and in predictions of 93 per cent in surviving animals

We gratefully acknowledge the aid of Dr C W de Lannoy Jr and Dr Aleksander Knezevich in helping to devise some of the techniques of the earlier experiments The authors are also indebted to Mr William Baughman Mr I Madigan and Mr J Lindsley for technical assistance We also wish to thank Mr D Lindgren for writing the computer program and Mr J Ito for doing the illustrations.

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Case reports

Friedreich's ataxia associated with idiopathic hypertrophic subaortic stenosis

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Friedreich's ataxia (FA) is a progressive neurologic disorder, frequently familial and most often beginning in childhood. In its classical form the disorder is characterized by spinal and cerebellar ataxia, diminution of the deep tendon reflexes, presence of extensor plantar responses, and the loss of appreciation for senses of vibration and touch. Optic atrophy is often present. Nonobstructive myocardial disease accompanies or may even precede the neurologic symptoms of this disorder.[1-10]

In idiopathic hypertrophic subaortic stenosis (IHSS) restriction in left ventricular filling and obstruction to left ventricular outflow are the main hemodynamic disturbances.[11-15] Its etiology is as obscure as the etiology of Friedreich's ataxia. The electrocardiographic abnormalities in this disease may be identical to those seen in Friedreich's ataxia, including arrhythmias, voltage evidence for left ventricular hypertrophy, and T wave changes.

Association of these two disorders has not been described, and the probability of their unrelated occurrence in the same patient is exceedingly small. We would like to present a patient with both these diseases; furthermore, we wish to report hemodynamic data of five additional patients with Friedreich's ataxia specifically studied for the presence of left and/or right ventricular outflow tract obstruction.

Case report

D. C., a Caucasian male patient, was born March 25, 1951. There was no family history of neurologic or cardiovascular diseases. The patient was first evaluated at the age of 10 years because he tired easily. There was no history of streptococcal infection or joint symptoms. Routine neurologic examination was normal, except that his gait was thought to be awkward. He did not show signs of congestive heart failure, and his peripheral pulses were normal. By palpation he had a slightly increased left ventricular impulse. The heart sounds were within normal limits. A Grade 2/6 apical pansystolic murmur with radiation to the axilla was heard. The chest X-ray was normal. The electrocardiogram (ECG) demonstrated borderline left ventricular hypertrophy and negative T waves in Leads 1, 2, aVF, and V_4 to V_6 (Fig. 1). The diagnosis of IHSS was suspected. Cardiac catheterization was performed at age 12 years (Table I). Arterial and venous blood oxygen content was normal. Pressures across the right heart were within normal limits. At rest, a 60 mm. Hg systolic pressure gradient between the left ventricular body (using a transseptal cathe

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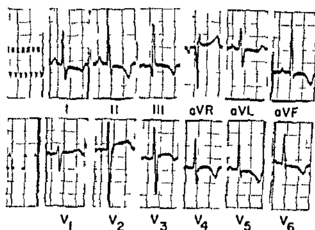


Fig. 1. Patient D. C. ECG demonstrating left ventricular hypertrophy and inverted T waves in Leads *I, II, aVF,* and V_4 to V_6. (Patient is not taking any *medication.*)

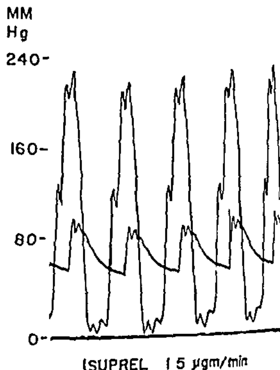


Fig. 2. Patient D. C. Tracing depicts simultaneous left ventricular and femoral arterial pressures during the infusion of Isuprel at a rate of *1.5 μg* per min. Note the notching of the ascending limb of the ventricular trace.

ter with 6 side holes and end hole) and the *femoral* artery (using a Cournand 18 G needle) existed only during postectopic ventricular contractions. Isuprel was infused at a rate up to 1.5 μg per minute, the left ventricular systolic pressure increased from 100 to 235 mm. Hg (Fig. 2) while femoral arterial systolic pressure fell from 100 to 85 mm. Hg. The left ventricular angiogram showed marked hypertrophy of the ventricular wall and moderate muscular subvalvar obstruction. During the following two years this patient complained of increasing *tiredness. At the age of 14 he underwent* cardiac surgery. At the time of thoracotomy cardiac enlargement was noted and was thought to be primarily due to an increase in muscle mass of the left ventricular wall. A systolic pressure gradient could again be demonstrated only during postectopic ventricular contractions. An aortotomy was performed. A region of the left ventricular outflow tract approximately 5 to 6 cm. below the aortic valve was narrowed by a hypertrophied group of anteriorly placed muscle bundles. Some of this muscle was removed, but the *major portion of the procedure consisted of enlarging* the outflow trough by the dividing and spreading of these muscle bundles. Histologically this muscle had the appearance of hypertrophy; there was no fibrosis, edema, *inflammation, or increased glycogen content.* Postoperatively the patient had two grand mal seizures. He required a respirator for 10 days. He left the hospital during the fourth postoperative week. At the time of his discharge his intelligence was normal. The neurologic examination demonstrated some right-sided weakness, some ataxia of the upper extremities, and absent deep tendon reflexes. These findings were initially thought to be compatible with basilar artery insufficiency incurred at the time of surgery. The diagnosis of Friedreich's ataxia was *made* subsequently when limb and truncal ataxia increased, when his speech became slurred, and when bilateral optic atrophy was noticed. In 1968, three years following surgery, the patient demonstrated *all the classical* findings of Friedreich's ataxia. At that time his left ventricle was still mildly enlarged. The heart sounds were *normal.* There was a Grade 2/6 ejection systolic murmur heard along the upper left sternal border. There was no longer a separate apical murmur. The ECG continued to show borderline left ventricular hypertrophy and *T wave inversion in Leads 2, aVF,* V_5 and V_6. Repeat cardiac catheterization (Table II) was normal; neither during postectopic ventricular contractions nor during Isuprel infusion (up to 6 μg per minute), nor during Valsalva maneuver and bicycle exercise was a pressure gradient present between the left ventricular body and the ascending aorta. Only the left ventricular end-diastolic pressure rose during Isuprel infusion from 9 to 16 mm. Hg. The cineangiogram demonstrated residual left ventricular hypertrophy but no obstruction of the out*flow tract.*

Methods of hemodynamic study of 5 patients with Friedreich's ataxia

Five patients of from 17 to 50 years of age with classical Friedreich's ataxia agreed to participate in a hemodynamic study of the possible relationship of this disease to IHSS. Informed consent was obtained in each case. All of these patients had typical electrocardiographic T wave changes but normal left precordial voltages. Cardiac catheterization was performed under local anesthesia using two venous and two

Table I Cardiac catheteri ation data of patient at age 12 with idiopathic hypertrophic subaortic stenosis and Friedreich s ataxia*

	RA†	RV	PA	Pc	LV	Ao	Heart rate (/min)	Q (l/min)
Rest								
Phasic	a = 10	26/9 ED	21/12		100/10 ED	100/60	95	4 [illegible]
Mean	6		18	11				
Postectopic ventricular contraction	—	—	—	—	110/15 ED	80/45	—	—
Isuprel 1 5 µg/min	—	—	—	—	230/15 ED	85/68	140	—

B A 1 39 M* w gh 47 6 kil gram Ge ral n thesia.
†Pr sure in mm Hg Abb e i tions RA = right at RV = r ght e tr l PA = pulmo ry t ry P = r lm nary cap llary
p ss re Ao = sce ding a rt LV = l ft t xl Q = ca d ts t BSA = body rfa e a ea ED = n l-d s tolic

Table II Cardiac catheteri ation data of patient at age 17 with idiopathic hypertrophic subaortic stenosis and Friedreich s ataxia*

	RA†	RV	PA	Pc	LV	Ao	Heart rate (/min)	Q (l/min)
Rest		27/6 ED	23/13		170/9 ED	170 85	90	5 5
Mean	6		17	9				
Postectopic ventricular contraction	—	—	—	—	170/[illegible] ED	120 85	—	—
Isuprel 6 µg/min	—	—	—	—	170/10 ED	175/80	160	—
5th min exercise (bicycle supine)	—	—	35/20	—	136/16 ED	135/90	150	10 7

BSA 1 69 M* w ght 58 3 k l gram Local sth a
†Pressures mm Hg Abb iatio RA = right trium RV = right e tricle PA = p lm ry rt ry P = p lm nary cap ll ry
p ss re A = sce d g ao t LV = left ve t l Q = l cout B A = body urface ea ED = end-dia t lic

arterial catheters to record simultaneously ascending aortic left ventricular pulmonary arterial and right ventricular pressures The Fick method was used for estimation of cardiac output An Isuprel infusion of up to 6 µg per minute was employed to enhance ventricular contraction Fifteen minutes following Isuprel infusion a right ventricular biplane cineangiogram (frontal and lateral projection) and a single plane left ventricular cineangiogram (RAO projection) were made Exercise studies were not undertaken because of the patients inability to perform coordinated leg movement

Case histories

Case 1 J S was born Jan 30 1943 She h four norm l ld l n an l no fam ly h tory of Friedreich s ataxia Her early development was normal unt l age 10 when she began to have difficulty with her balance At age 14 she could no longer walk un as i ted Her understanding is normal but she has ataxic speech her fundi are normal There i marked *ataxia of trunk* and extremities she can type and feed herself but i restricted to a wheelchair Proprioception is still present but *markedly dimin hed* Deep tendon reflexes are absent *plantar respon es* are exten or She has pes cavus and some scolio i of the spine Physical examination of the cardiovascular system *revea s s ightly* weak but symmetrical peripheral pulses She has a *normal* apical impulse S is of normal intensity S₂ i physiologically split Murmurs cannot be heard The ECG shows a normal sinus rhythm and an indeterminate axis the precor lial voltages are normal *the T* waves are flat biphas c in Leads I aV F V₅ and V₆.

Case 2 L D was born Dec. 30 1937 she i the oldest of five children *One brother* (Patient No 3) has Friedreich s ataxia By age 5 her gait was unsteady and her speech lurred At age 15 she was confined to a wheelchair At age 16 diabetes mell tus

Table III. Sex, age, family history, and ECG data of 5 study patients with Friedreich's ataxia (F.A.)

Patient	*Sex*	*Age at onset of F.A.*	*Age at hemodynamic study*	*Family history*	*ECG data*
1	F	10	27	Normal	T flat in I, aVF, and V_5 to V_6
2	F	5	33	Sibling of Patient 2	T ↓ in I, aVF, V_5 to V_6, and PAC
3	M	9	21	Sibling of Patient 3	T ↓ in V_5 to V_6 and PAC
4	F	6	17	Normal	T ↓ in I, aVF, and V_4 to V_6
5	M	15	50	Sister with F.A.	T ↓ in aVF and V_4 to to V_6, 1° AV block (takes digitoxin because of history of supraventricular tachycardia)

was diagnosed and she has required 25 units of NPH daily. Now at age 35 there is a marked kyphoscoliosis. She is almost completely unable to move; she cannot feed herself, talk intelligibly, or see even the largest objects. There is bilateral optic atrophy, absence of deep tendon reflexes, pes cavus, and bilateral extensor plantar responses. The cardiovascular examination is normal. S_1 is normal. S_2 splits normally. S_3 is not present, and there is a Grade 2 short ejection systolic murmur at the second and third left intercostal spaces. The ECG shows right axis deviation, sinus rhythm with premature atrial beats, and T wave inversion in I, II, aVF, and V_4 to V_6.

Case 3. D. D., the brother of *Patient No. 2*, was born May 13, 1948. His development was normal until age 9 when he first became unsteady. Since then he has had progressive ataxia so that now at age 21 he can no longer walk without assistance. His speech is ataxic. He has bilateral optic atrophy, absent deep tendon reflexes, extensor plantar responses, and moderately severe kyphoscoliosis. The heart is normal in size. S_1 and S_2 are normal; there is a Grade 2 short ejection systolic murmur present in the second left intercostal space. The ECG demonstrates a sinus rhythm with occasional premature atrial beats. S waves in V_5 and V_6 suggest right ventricular hypertrophy. The T waves are inverted in V_5 and V_6.

Case 4. J. C. was born Sept. 2, 1953. *She has three* older siblings and one younger, all healthy. Symptoms of ataxia first appeared at age 6. Bilateral arthrodeses were performed at age 15, enabling her to walk with assistance. She has *marked truncal and* limb ataxia, ataxic speech, bilateral optic atrophy, absent deep tendon reflexes, and the plantar responses are extensor. The heart is normal in size. S_1 and S_2 are normal; *a Grade 2 ejection systolic murmur* is present along the left upper sternal border. The ECG demonstrates a normal sinus rhythm and negative T waves in Leads I, II, aVF, and V_4 to V_6.

Case 5. W. C. was *born Mar. 2, 1920*. He has three siblings, but only the older sister has Friedreich's ataxia. He was 15 when he first became ataxic. By age 26 he was limited to a wheelchair but is at age 50 able to move about in the chair. He has marked truncal and limb ataxia, dysarthric but intelligible speech, absent deep tendon reflexes, and extensor plantar responses. He does not have optic atrophy. In 1967 he was given digitalis because of atrial tachycardia with 2:1 and 3:1 block. His heart is normal in size. S_1 and S_2 are normal; there is an apical S_3. A Grade 2 ejection systolic murmur is present along the left sternal border. The ECG now shows a sinus rhythm and first degree AV block. Negative T waves are present in Lead II, aVF, and V_4 to V_6.

Results

Age distribution and hemodynamic data of the five study patients are presented in Tables III and IV. Significant intracardiac shunts were excluded in each case by oxygen saturation data and angiography. The cardiac index at rest ranged from 1.8 *to 3.1 L. per min. per M.² Resting pres*sures were normal in both the left and right heart except in patient No. 4 who had a left ventricular end-diastolic pressure of 16 mm. Hg. Systolic pressure gradients were absent at rest as well as after ectopic ventricular contractions. During Isuprel infusion heart rates increased 30 to 70 beats per minute (average 42 beats). Only 1 patient (Case 5) developed a peak systolic left ventricular-aortic *pressure gradient* of 40 mm. Hg. In patient No. 3 Isuprel induced a 16 mm. Hg peak systolic gradient between the right ventricular body and pulmonary artery. In each patient the cineangiogram demonstrated increased left

ventricular wall thickness Two patients (Cases 2 and 4) had an abnormally shaped left ventricular cavity at end systole the left ventricular chamber was incompletely divided by prominent muscle ridges into a slitlike apical portion and a small conical subaortic portion These same two patients also showed pronounced contractions of the right ventricular outflow tract without systolic pressure gradients The angiogram of Case 5 showed a dilated left ventricular chamber with an apparently normal outflow tract poor contractility and a larger than normal end systolic volume Two patients (Cases 1 and 4) had distinctly dilated right coronary arteries The patient with IHSS had dilatation of both right and left coronary arteries None of the patients had angiographic evidence for narrowing of the coronary artery branches

Discussion

The association of Friedreich's ataxia and idiopathic hypertrophic subaortic stenosis is highly intriguing Both disorders have a familial incidence and affect the myocardium Both become symptomatic approximately in the same age group Electrocardiographic evidence for left ventricular hypertrophy and T wave abnormalities are common to both diseases Yet the association of these disorders in one patient has not been reported

Myocardial disease combined with degenerative disease of the central nervous system has been reported with certainty only in Friedreich's ataxia and in Refsum's disease[14] Friedreich[2] himself described hypertrophy and fatty degeneration of the myocardium in some of his patients Pitt[8] emphasized the association of Friedreich's ataxia and heart failure The onset of cardiac symptoms and their severity are extremely variable Usually they develop long after the neurologic disorder is manifest rarely does congestive heart failure precede the onset of neurologic signs[9] Palpitations and retrosternal chest pain have been the chief cardiac symptoms As many as 90 per cent of the patients have electrocardiographic abnormalities which include atrial and ventricular arrhythmias and negative T waves in Leads I II aVF and V_1 to V_3 Three of our patients had premature atrial contractions and all patients had the typical T wave abnormalities While left ventricular hypertrophy has been reported for almost half of the patients with Friedreich's ataxia none of ours demonstrated abnormally tall R waves in the left precordial leads

Hemodynamic studies done in patients with Friedreich's ataxia have demonstrated moderate degrees of ventricular dysfunction The mean pulmonary capillary pressure and left ventricular end diastolic pressures have been reported as elevated (larger than 10 mm Hg) in patients with advanced neurologic disease[10] Two of these patients had selective cineangiograms which demonstrated pronounced contractions of the right ventricular outflow tract with a delayed washout of contrast material Muscular hypertrophy with dilatation of the left ventricle was also present In another study[17] a 34 mm Hg systolic pressure gradient across the left ventricular outflow tract was induced by Isuprel infusion The angiogram of this case demonstrated dilatation and hypertrophy of the left ventricle

In our study left ventricular hypertrophy was common to all patients Two patients had abnormal degrees of left ventricular contractions at end systole the left ventricular chamber appeared incompletely divided into a slitlike apical and a small conical outflow portion however significant pressure gradients were not present

Diffuse myocardial hypertrophy is common to both IHSS and Friedreich's ataxia In IHSS it involves chiefly the ventricular septum and the left ventricular outflow tract The absence or presence of a pressure differential between left ventricular body and aorta depends on the functional behavior of the outflow tract Increased ventricular wall thickness correlates with increased ventricular filling pressure noted in both diseases when an advanced stage is reached and it is then associated with a low cardiac output Angiographically the ventricular end systolic volume may be small and ventricular contractions may appear to be forceful in both IHSS and Friedreich's ataxia While a pressure gradient between the left ventricle and the aorta either at rest or during Isuprel infusion is as implied by the name part of

Table IV. Hemodynamic data of 5 study patients with Friedreich's ataxia

Patient	Rest							
	Heart rate (min.)	Cardiac index (L./min./M.²)	Stroke index (ml./M.²)	Pressures (mm. Hg)				
				Pc	PA	RV	Ao	LV
1 J. S.	70	2.9	42	—	22/6	22/4	110/75	110/10
2 L. D.	80	1.8	23	5	18/10	20/10	95/60	100/1
3 D. D.	85	3.0	35	11	24/10	24/8	110/85	110/1
4 J. C.	100	3.1	31	11	22/12	22/9	100/65	100/
5 W. C.	90	2.5	28	7	26/8	26/4	140/80	140/10

Abbreviations: Pc = pulmonary capillary pressure; PA = pulmonary artery; RV = right ventricle; Ao = ascending aorta; LV = left ven...

IHSS we have found it only in two out of six patients with Friedreich's ataxia. However, the obstructive component of IHSS may not always be present and the restrictive component (restriction to ventricular filling) may be of even greater clinical significance.[11]

It is apparent that there are distinct clinical and hemodynamic similarities in cardiomyopathy of Friedreich's ataxia and IHSS and a comparison of the histological changes of these diseases is of interest. In Friedreich's ataxia the myocardium shows diffuse reticular fibrosis; the myocardial fibers are hypertrophied and also display degeneration with decreased cross striation and fatty metamorphosis.[10,18] In some cases[19] mononuclear cell infiltration and vacuolated and hyperchromatic nuclei have been seen. The coronary arteries may show all stages of intimal proliferation to the point of obstruction.[10,18,19] In IHSS myocardial hypertrophy and fibrosis are equally prominent findings; bundles of abnormally thick but short muscle fibers show a bizarre disorderly arrangement and are separated by an increased amount of connective tissue, often with considerable fibrosis.[20] There may be extensive though focal degenerative changes with peripheral mononuclear cell infiltrates.[21] Individual muscle fibers vary considerably in thickness and show dystrophic changes and proliferation of sympathetic nervous fibers is evident.[2] The coronary arteries have been reported to be dilated,[12,3] but are otherwise normal.[1] Teare[20] noted repeatedly a smaller than normal number of branches coming from the left anterior descending coronary artery, but was not certain whether this was an artifact (related to the method of injection with radiopaque material) or a real finding.

While the incidence of functional subaortic stenosis is higher in IHSS and the degree of obstruction much more severe than in Friedreich's ataxia, the similarities in myocardial changes as well as in hemodynamics and clinical expression of heart disease are striking. A relationship of the respective etiological factors is a fascinating speculation.

Summary

Friedreich's ataxia and idiopathic hypertrophic subaortic stenosis (IHSS), both diseases of unknown etiology, both result in hypertrophy and degenerative changes of the myocardium. Both diseases lead to nearly identical electrocardiographic changes. We report a patient who developed classical signs of Friedreich's ataxia several years after he was found to have moderately severe IHSS. This observation

	Isuprel i fusion				
rt te min	*Pressures (mm Hg)*				*Angiographic data*
	P A	*RV*	*Ao*	*LV*	
40	30/6	30/4	110/50	110/10	Increased left ventricular wall thickne s Dilated ri ht coronary artery
10	23/6	23/4	85/50	90/10	Increased left ventricular wall thicknes Extreme systol c contraction
?0	?6/1?	4?/10	115/83	115/ 0	Increased left ve tricular wall th ckness
?0	17/11	17/8	105/75	105/16	Increa ed left ventricular wall thickne Extreme systolic contractions Dilated right coronary arteries
30	?8/8	?8/5	130/80	1?0/10	Increased left ventricular wall thickness Poor sy tolic contractions Moderate left atrial and left ventricular enlargement

prompted a hemodynamic study of five other patients with Friedreich s ataxia in search of a more common association and thus a possible etiological link between the two diseases Cardiac catheterization was performed under local anesthesia Catheters were inserted into the right ventricle the pulmonary artery the left ventricle and the aorta Isuprel infusion up to 6 µg per minute was used in an attempt to induce an abnormal pressure gradient across the right or left ventricular outflow tract Both right and left ventricular cineangiograms were obtained for evaluation of ventricular kinetics and wall thickness Right and left heart pressures were normal at rest in all patients During Isuprel infusion a 40 mm pressure gradient was induced across the left ventricular outflow tract in only one patient A second patient developed a 16 mm gradient across the right ventricular outflow tract All patients had low normal cardiac outputs The angiograms demonstrated increased left ventricular wall thickness in all patients It is concluded that systolic left and/or right ventricular outflow tract obstruction is only infrequently present in Friedreich s ataxia and is mild in degree An etiological link between Friedreich s ataxia and IHSS is not known at the present but may po sibly exist and should be investigated

Addendum

After this paper had been accepted for publication a first and single case report of hypertrophic obstructive cardiomyopathy associated with Friedreich s ataxia has appeared in the *American Journal of Cardiology* 27 436 1971

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Congenital pulmonary and subclavian arteries steal syndrome

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Cerebrovascular insufficiency produced as a result of reversal of blood flow in the vertebral artery secondary to occlusion in the proximal subclavian or innominate arteries is referred to in the literature as the subclavian steal syndrome.[1-3] In the majority of cases, the central nervous system symptoms are secondary to acquired retrograde flow in the vertebral artery. Congenital subclavian artery steal syndrome has been described secondary to stenosis or atresia of the intrathoracic portion of the subclavian artery.[4-7] Acquired subclavian steal has been noticed after the Blalock-Taussig operation.[8] Recently, an infant was seen at Albany Medical Center Hospital with central nervous system symptoms and signs. Auscultation of the heart revealed a continuous murmur to the left of the sternum. Cardiac catheterization and angiocardiography demonstrated retrograde blood flow in the left vertebral and left common carotid arteries, secondary to anomalous communication between these two vessels and the pulmonary artery. The object of this paper is to report this interesting case.

Case report

T. R., a 7 month old infant, had been admitted to Albany Medical Center Hospital at the age of 2 days for multiple congenital anomalies. The mother had had a severe infection in the upper respiratory tract during the fifth month of her pregnancy. Delivery was at term and uneventful and the birth weight was 5 pounds and 5 ounces. Amniotic fluid was reportedly excessive, and low set ears, peripheral paralysis of the right side of the face, and choanal atresia were noted at birth. The family history revealed that the parents were both 27 years old. Two other siblings, ages 5 and 4 years, were alive and well. On physical examination, the infant was small and abnormal looking, and had a head circumference of 35.5 cm., which was at the fiftieth percentile. The anterior fontanel was open and soft and the sutures were overriding. The patient was unable to close the right eyelid and was unable to move the right side of the mouth. The right ear was grossly deformed. There was apparent choanal atresia in the right nostril with thick white secretions. The mandible was small and the infant had a

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(Fig 4) The left side of the heart was entered from the right atrium through an atrial septal defect. The ascending aorta arose from the left ventricle and formed a right sided aortic arch and thoracic aorta The aortic arch gave origin to two branches—the right common carotid and the right subclavian arteries There was no apparent connection between the ascending aorta or the right aortic arch and the vessel to the left of the spine that gave origin to the left common carotid and the left subclavian arteries (Fig 5) A small vessel however connected the right thoracic aorta to the pulmonary artery Selective injection of dye into the left ventricle and right aortic arch opacified the right common carotid and right vertebral arteries and the ipsilateral cerebral vessels A few seconds later the left common carotid and the left subclavian arteries were seen to opacify retrogradely from the cerebral circulation From these two vessels the large vessel to the left of the spine and the pulmonary artery opacified (Fig 6)

After cardiac catheterization the patient underwent thoracotomy for a possible vascular ring The small vessel which connected the right thoracic aorta to the main pulmonary artery was identified as a small right patent ductus arteriosus and was divided The large vessel which arose from the pulmonary artery and gave origin to the left common carotid and left subclavian arteries was identified as the left dorsal (thoracic) aorta. Since the blood flow in this vessel was in a retrograde fashion the vessel was ligated at its junction with the pulmonary artery The child died after the operation was completed

At autopsy the left cerebral hemisphere was slightly smaller than the right hemisphere Similarly the vertebral artery on the left was smaller than the one on the right. There was a Meckel s diverticulum 34 cm. proximal to the cecum and it measured 1.3 cm Microscopically it showed gastric mucosa in one region. The heart was slightly enlarged and weighed 130 Gm. The great arteries were normally situated but the pulmonary artery appeared to be slightly larger than the aorta The aortic arch and thoracic aorta were situated on the right side (Fig 7) The aortic arch gave origin to the right common carotid and the right subclavian arteries The pulmonary artery gave rise to four branches—the right and left pulmonary arteries the left dorsal (thoracic) aorta and a small right patent ductus arteriosus. The latter two vessels had been ligated surgically at their origin from the pulmonary artery Superiorly the left dorsal (thoracic) aorta divided into the left common carotid and the left subclavian arteries. The right ductus arteriosus connected the pulmonary artery to the junction between the right aortic arch and the right thoracic aorta. There was an ostium secundum atrial septal defect that measured 5 by 5 mm The systemic and pulmonary veins and the coronary arteries were normal



Fig Chest x ray film at 2 days of age shows no cardiac enlargement and normal pulmonary vascularity The aortic arch is probably situated on the right side

Table I Cardiac catheterization

Site	Oxygen saturation (%)	Pressure (mm Hg)
Superior vena cava	46	
Inferior vena cava	63	
Right atrium	60	2
Right ventricle	—	35/0
Pulmonary artery	74	35/10
Left atrium	94	2
Left ventricle	92	80/10
Left dorsal aorta	93	40/35

Discussion

The primary embryonic arteries are the right and left primitive aortae According to Hamilton Boyd and Mossman[8] each primitive aorta can be readily divided into three portions (1) a short ventral ascending portion (2) a primitive (first) aortic or pharyngeal arch artery and (3) a relatively long descending portion which distributes the blood from the heart to the embryonic tissues When the process of fusion of the endothelial cardiac tube reaches the anterior limit of the pericardial cavity it extends forward to involve the cardiac extremities of the two ventral aortae As a result the bulbus cordis is continuous cranially beyond the pericardium with a single midline vessel called the truncus arteriosus or aortic sac The right and left first aortic arch arteries arise from this vessel With the formation of further pharyngeal arches the first pair of aortic arch arteries is supplemented by the successive addition of five more pairs one in each of the arches The dorsal aortae fuse toward their caudal extremities to form a

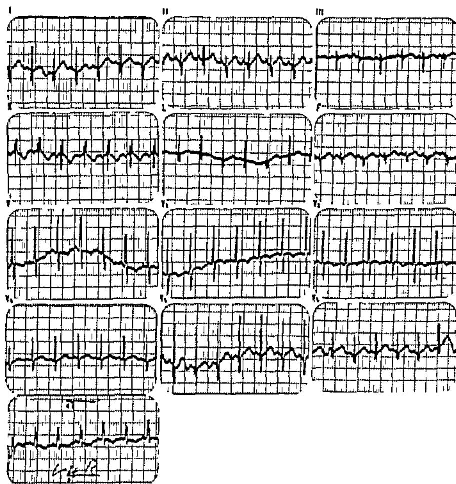


Fig. *1* Electrocardiogram at 2 days of age shows left axis deviation

poor suck and a poor cry The tongue and pharynx appeared to be normal Examination of the lungs revealed coarse rhonchi throughout Examination of the cardiovascular system revealed a markedly diminished left brachial pulse and almost no left carotid pulse On auscultation of the heart the second sound was single and a soft ejection murmur was heard in the pulmonary area There was no evidence of hepatosplenomegaly Examination of the extremities revealed digitalization of the thumb and the fourth and fifth digits were noted to overlap There was a wide space between the first and second toes The electrocardiograph showed a left axis deviation but there was no evidence of abnormal ventricular hypertrophy (Fig 1) The chest x ray film suggested a right aortic arch (Fig 2) The urine analysis was within normal limits and the electrolytes glucose and blood urea nitrogen were normal The hemoglobin was 14 6 Gm hematocrit 47 and white blood count 7 000 The cerebrospinal fluid was clear and not under tension The sugar was 66 mg protein 87 mg and cell count 1 000 fresh and crenated red blood cells No white cells were seen Cultures were negative Skeletal examination of both hand demonstrated no bony architectural abnormalities Since the infant was unable to swallow he was fed by tube Chromosome studies revealed no anomalies detectable in the peripheral smear Laboratory tests ruled out toxoplasmosis rubella and cytomegalic inclusion disease Urinary and serum amino acids were also normal

The patient remained in the hospital was fed by tube and was given antibiotics from time to time because of recurrent chest infections When he was 2 months old the cardiovascular system was reassessed and a Grade 2/4 continuous murmur was noted beneath the left clavicle In addition the left subclavian and carotid pulses were impalpable The electrocardiogram showed deep Q waves in Lead V_{5-6} suggesting left ventricular hypertrophy (Fig 3) The chest x ray film showed increased pulmonary vascularity Since the combination of a continuous murmur and a lack of left subclavian and left carotid pulses suggested a vascular abnormality and possibly a vascular ring cardiac catheterization was performed through the right femoral vein on Sept 17 1968 The pressure and samples are shown in Table I The pressures in the right ventricle and pulmonary artery were slightly elevated A left to-right shunt was observed at the atrial and pulmonary arterial levels While in the pulmonary artery the catheter intubated a vessel to the left of the vertebral column The pressure in this vessel was equal to that in the pulmonary artery but the blood in it was 93 per cent saturated with oxygen Superiorly this vessel bifurcated and gave origin to the left subclavian and the left common carotid arteries Inferiorly this vessel terminated in the main pulmonary artery

single midline vessel lying between the developing gut ventrally and the notochord dorsally. The first pharyngeal arch arteries disappear at about the time that the third arch arteries are fully differentiated. Involution of the second arch arteries follows as the fourth arch arteries mature and increase in size. The fifth pair is never well developed and its arteries are present for only a very short time. At the end of the somatic period the sixth arch arteries give off descending branches to the plexuses of the lung buds and are called pulmonary arches. Later during the course of development the truncus arteriosus is divided by the spiral septum in such a way that the blood from the right ventricle comes to empty into the sixth arches while that from the left ventricle is distributed to the third and fourth arteries. At a later stage of development the segment of the dorsal aorta between the third and fourth arches on each side disappears. At the same time the segment of the right dorsal aorta between the right fourth artery and its junction with the left dorsal aorta and the lateral portion of the right sixth arch artery disappear. Blood from the heart can now pass to the single descending aorta only by way of the left fourth and sixth arch arteries. The terminal part of the latter persists as the ductus arteriosus until full term. The aortic sac, its left horn and the left fourth arch artery form the arch of the definitive aorta. The right horn of the aortic sac elongates to become the innominate artery, which terminates by giving origin to the right third and fourth arch arteries. The former of these branches becomes the right common carotid artery and the commencement of the right internal carotid artery. The right fourth arch artery forms the stem of origin of the right subclavian artery. The left subclavian artery arises by the hypertrophy of a segmental branch of the left dorsal aorta.

It would seem therefore that the embryological explanations of the congenital vessel anomalies of our patient could be as follows. The right and left dorsal aortae have persisted. The point of communication between the left dorsal aorta and the pulmonary artery must represent a left patent ductus since the only way a systemic artery can communicate with the pulmonary artery

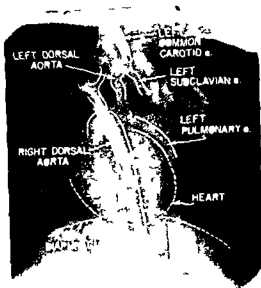


Fig. 6. An aortic root angiogram. This frame was taken a few seconds after that shown in Fig. 5. Notice retrograde filling of the left common carotid and left subclavian arteries. These two vessels fed the large artery which arose from the pulmonary artery.

is through a patent ductus. Our patient therefore had a right and a left patent ductus arteriosus. Disappearance of the segment of the left thoracic aorta beyond the left sixth arch would account for the presence of a right descending aorta. The right aortic arch must have developed from the right fourth arch artery and the right common carotid artery from the right third arch artery. The right subclavian artery must have developed from a segmental branch of the right dorsal aorta. Since there was no communication at any level between the two thoracic aortae the left fourth arch artery probably had not developed at all and the left subclavian artery must have developed from hypertrophy of a segmental branch of the left thoracic aorta.

Clinical evaluation of the central nervous system of the patient during life demonstrated a right peripheral nerve palsy and dysphagia. In all probability these two conditions were not related to the vascular problem. The facial palsy was probably traumatic and the dysphagia secondary to choanal atresia. As pointed out by other workers[4,7] central nervous system signs are uncommon in the congenital variety of the

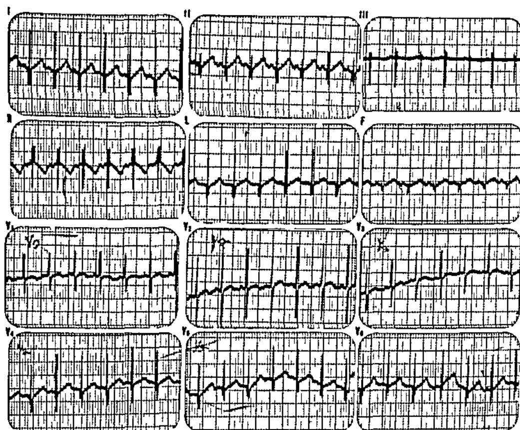


Fig 3 Electrocardiogram at 2 months of age shows left axis deviation and deep Q waves in lead V6.

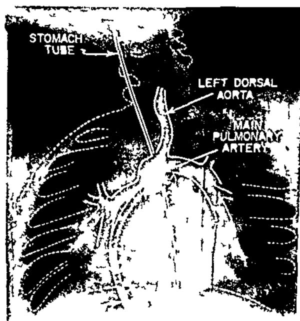


Fig 4 A pulmonary arterial angiogram shows a large vessel that originated from the pulmonary artery to the left of the spine

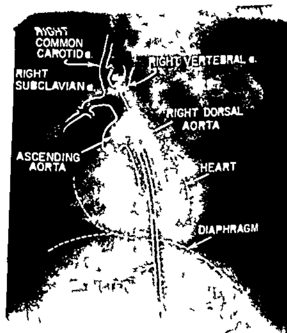


Fig 5 An aortic root angiogram shows right aortic arch and right thoracic aorta. Note opacification of the right subclavian, right common carotid and right vertebral arteries

Summary

A 2 month old infant was seen at Albany Medical Center Hospital with right peripheral facial palsy and dysphagia Evaluation of the cardiovascular system showed a lack of left common carotid and left subclavian pulses A continuous murmur was heard to the left of the sternum Cardiac catheterization and angiography demonstrated retrograde filling of the left common carotid artery the left subclavian artery a left dorsal aorta and the pulmonary artery from the opposite side of the cerebral hemisphere Autopsy revealed a right aortic arch and a right thoracic aorta The right common carotid and right subclavian arteries arose from the right aortic arch A large left dorsal aorta arose from the pulmonary artery and divided superiorly into the left common carotid and the left subclavian arteries There was no communication between the two aortae The central nervous system signs were thought not to be secondary to pulmonary artery steal It was suggested that a lack of pulses and a continuous murmur would suggest such a diagnosis

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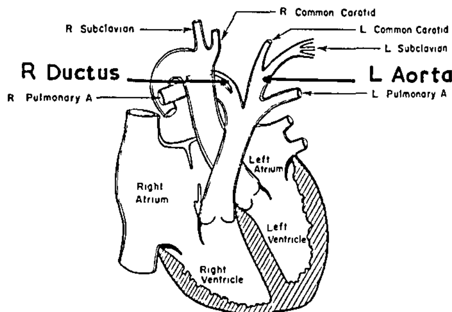


Fig. 7 Diagrammatic illustration of the cardiac findings at autopsy

subclavian artery steal In this context, we have to emphasize that, in the congenital variety of this syndrome, the steal is from the basilar system In our patient the steal was from both the basilar system and the circle of Willis

Although cardiac catheterization and selective angiocardiography demonstrated that the left common carotid artery, left subclavian artery, and left dorsal aorta were being fed by blood from the opposite cerebral hemisphere, the pathophysiology of this congenital abnormality did not become clear to us until after surgery and autopsy The shunt at the pulmonary arterial level had been interpreted as a patent ductus arteriosus but we could not explain the low pressure in the left thoracic aorta and its two branches A vascular ring was thought to be the most plausible explanation Undoubtedly the fact that this condition has not been described before explains the difficulties we have had in making the diagnosis during life

The various conditions which can give rise to a continuous murmur to the left of the sternum are well recognized To the best of our knowledge, a continuous murmur caused by pulmonary artery steal has never been described before The etiology of this murmur in our patient was probably the continuous flow of blood from the left dorsal aorta to the pulmonary artery throughout the two phases of the cardiac cycle Blood flow through the right ductus must have also contributed to this murmur

We believe that "pulmonary and subclavian arteries steal syndrome" should be suspected when there is a continuous murmur to the left of the sternum and a lack of carotid and brachial pulses Only cardiac catheterization will demonstrate a left to right shunt at the pulmonary arterial level and low pressure in the common carotid and subclavian arteries Angiography of the opposite carotid artery should establish the diagnosis since it will demonstrate retrograde blood flow in the carotid and vertebral arteries of the affected side Moreover delayed opacification of the pulmonary artery should be observed We believe that the anatomic anomalies described here are probably extremely rare On the other hand the basic physiologic concept of the pulmonary and subclavian arteries steal should not be all that rare and probably various combinations of anomalies of the aortic arches would give rise to the same clinical picture It is suggested therefore, that this condition should be suspected in any patient who has unilateral absence of the carotid and subclavian pulses and a continuous murmur Surgical ligation of the pulmonary end of the anomalous vessel and anastomosis of its distal end to the aorta should correct the hemodynamic abnormalities



Fig 1 Thoracic roentgenogram

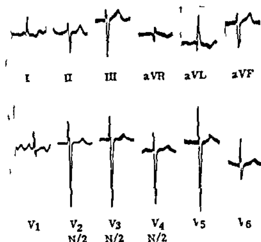


Fig 2 ECG

restriction of salt intake and administration of diuretics and digitalis.

At the age of 20 years the patient was admitted for further studies so as to determine whether further surgical intervention was possible and advisable A moderate degree of congestive cardiac failure was recognized The hemoglobin was 16 5 Gm. per 100 ml of blood Since this was considered a relatively low level for a cyanotic patient she was treated with oral iron replacement with a subsequent rise in the hemoglobin level to 21 5 Gm per 100 ml of blood This in turn was associated with improvement in her clinical condition although signs of congestive failure remained The physical findings remained unchanged with the patient showing marked cyanosis.

DR ROBERT A VAN TASSEL Perhaps Dr Amplatz will show the x rays

DR KURT AMPLATZ This is a roentgenogram taken when the patient was 20 years old (Fig 1) The cardiac silhouette is grossly enlarged with biventricular prominence There is pectus carinatum The left hemidiaphragm is elevated In the left pleura there are prominent signs of effusion and or pleural thickening with pleural effusion being the most likely possibility The pulmonary vascularity is normal and there is no evidence of a left to right shunt Scoliosis is very evident

DR VAN TASSEL Thank you Dr Amplatz Dr Moller would you care to look at the electrocardiogram (ECG) (Fig 2) from the patient s last admission and interpret it for us?

DR JAMES H MOLLER The rhythm is that of atrial fibrillation with occasional premature ventricular contractions Left axis deviation associated with a counterclockwise rotation of the QRS loop in the frontal plane is present There is no specific pattern of ventricular hypertrophy although the major forces are posteriorly directed S T and T wave changes are present

DR VAN TASSEL I shall continue with the admission when the patient was 20 years old A spleen and liver scan was normal Studies revealed a large right sided Blalock Taussig anastomosis The pressure in the ascending aorta was 100/65 mm Hg

From the aorta the catheter was advanced into the right pulmonary artery through the Blalock Taussig anastomosis The pressure in the right pulmonary artery was found to be 80/50 mm Hg and the mean pressure 60 mm Hg No further operation was advised

Two months after the final admission and while in a state of congestive cardiac failure the patient died in her home community

Dr Moller will you discuss the differential diagnosis?

DR MOLLER This young adult who died at the age of 20 years showed cyanosis in the neonatal period which then persisted throughout her life One of the most prevalent causes of cyanosis in the neonatal period is complete transposition of the great vessels The majority of patients with this condition die within the first few months of life The persistence of cyanosis however over a long period of time starting from the neonatal period is most commonly

Clinical pathologic conference

Robert A. Van Tassel, M.D.
Kurt Amplatz, M.D.
James H. Moller, M.D.
Franklin H. Martin, M.D.
Jesse E. Edwards, M.D.
St. Paul, Minn.

Case report

DR. ROBERT A. VAN TASSEL: A female child, when born to a diabetic mother after 36 weeks' gestation, weighed 8 pounds, 13 ounces. Cyanosis was noted at birth and persisted throughout her life. Both growth and development were retarded. At the age of 18 months, cardiac catheterization was performed and, although the results were inconclusive, a tentative diagnosis of pseudotruncus arteriosus was made. Complaints of dyspnea on exertion and fatigue were first elicited when she began school. The results of a second cardiac catheterization performed at the age of 8 years again were inconclusive but suggested pseudotruncus arteriosus. At this study, however, it was established that there was continuity of the inferior vena cava with the azygos vein and connection of a left superior vena cava with the left atrium. Following this catheterization procedure, the patient developed thrombophlebitis in the right leg, which was used for the study, and she experienced an episode diagnosed as pulmonary embolism. Although she recovered from this episode, permanent swelling of the right leg remained. At the age of 9 years, for reasons not clear in the record, digitalis and a diuretic therapy were initiated.

At the age of 14 years, the patient was referred to the University of Minnesota Hospitals for further cardiac evaluation because of an increasing degree of cyanosis. Additional history revealed increasing dyspnea, decreasing exercise tolerance, the onset of dizzy spells, and substernal chest pain which occurred with exercise. Physical examination revealed a small, frail, cyanotic female child. She was 58 inches tall and weighed 38.2 kilograms. The blood pressure was 126/70 mm. Hg, and the pulse was 68 beats per minute and irregular. The femoral pulses were normal. Both the finger and the toes revealed prominent clubbing. Marked scoliosis of the thoracolumbar spine was noted and associated with significant thoracic deformity. The lungs were clear and the precordium active. The point of maximal impulse was at the sixth intercostal space in the left anterior axillary line. A suprasternal thrill was present. The first cardiac sound was prominent and the second sound was single and of normal intensity. A Grade 2/6 systolic ejection murmur was present over the entire precordium but heard best below the left clavicle. A Grade 1/6 low-pitched diastolic murmur was heard over most of the precordium. The splenic tip was palpable on deep inspiration but the liver was not considered to be enlarged. The right leg was markedly swollen and the superficial veins were distended. Minimal swelling in the left ankle was present.

Cardiac catheterization was performed during this admission also. This study identified the venous anomalies previously observed and also revealed signs of tetralogy of Fallot with pulmonary atresia. The pulmonary artery was neither visualized on angiography nor entered with the catheter during the procedure. One year later, at the age of 15 years, a Blalock-Taussig anastomosis was performed on the right side. At operation, the surgeon noted the right pulmonary artery to be 12 mm. wide and under low pressure. The right subclavian artery, which was 5 mm. in diameter, was connected to the right pulmonary artery by an end-to-side anastomosis. The patient improved following operation; she showed less cyanosis and improved exercise tolerance. Six weeks following the operation, however, the patient was noted to be in a state of congestive heart failure for which she was treated with

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to development of pulmonary hypertension although it would not be severe since the child did not show a pattern of pulmonary edema

In summary I think the child has the polysplenic syndrome with an endocardial cushion defect and tetralogy of Fallot The lungs will show occlusive pulmonary vascular disease

DR VAN TASSEL Thank you Dr Moller Dr Martin would you please describe the necropsy findings?

DR FRANKLIN H MARTIN At necropsy the findings of major significance included both venous and cardiac anomalies

There was thoracic kyphoscoliosis with the convexity of the spine directed toward the right The mediastinal structures were shifted slightly toward the left Each pleural cavity was obliterated by dense fibrous adhesions Each lung possessed two lobes and the left lung was hypoplastic (Fig 3) The heart was enlarged with its apex being midline in type Major anomalies of the systemic veins were present

Within the heart two complexes were present namely the complete variety of persistent common atrioventricular canal (so called endocardial cushion defect) and the tet logy of Fallot

The former was characterized by (1) a large defect in the lowermost portion of the atrial septum (2) clefts in the septal tricuspid and in the anterior mitral leaflets yielding a common atrioventricular valve and (3) a defect of the ventricular septum leading to subvalvular interventricular communication (Fig 4)

Above the atrial septal defect which was part of the persistent common atrioventricular canal the atrial septum showed an additional opening of about 1 0 cm in diameter This opening was in the position of interatrial ostium II No distinct fossa ovalis could be identified

Although the right atrial appendage was somewhat larger than the left each was characterized by being relatively long compared to the width Muscular ridges were present in each but neither showed features characteristic of pectinate muscles A small organized thrombus was present in the right appendage (Fig 4 a)

The lining of each ventricle particularly

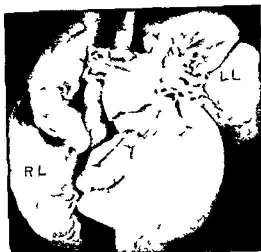


Fig 3 Thoracic organs viewed from in front The right lung (*R L*) is bilobed as is the left lung (*L L*) The latter is hypoplastic. The apex of the heart is midline in type

the left was unusually trabeculated (Fig 4 *b*) The outflow tract of the right ventricle was narrow by virtue of a vertical crista (Fig 5 *a*) The narrowed infundibulum led to the pulmonary valve The latter was bicuspid dome shaped and highly stenotic (Fig 5 *b*) Behind the vertical crista the aorta straddled the defective ventricular septum as it arose from both ventricles Continuity existed between the aorta and the anterior leaflet of the common atrioventricular valve

Of additional interest were the systemic veins (Fig 6) The inferior vena cava was abnormal in its course and position In the abdomen it lay to the left of the aorta (Fig 6 *a*)

Above the renal veins the inferior cava deviated toward the right but failed to pass through the liver Instead it entered the right hemithorax to become continuous with the azygos vein The latter which was unusually wide joined the right superior vena cava (Fig 6 *b*) The hepatic veins joined to form a common hepatic vein which in turn joined the right atrium where normally the inferior vena cava enters

There were two superior venae cavae The left which received the hemiazygos vein joined the left atrium directly (Fig 6 *c*) and the right entered the right atrium in the usual position In the superior medi

associated with tetralogy of Fallot or a condition closely related functionally such as single ventricle with pulmonary stenosis. Although unusual, there are a few instances of tricuspid atresia with cyanosis in the newborn period and survival of the patient for as long as 20 years. At cardiac catheterization this patient was found to have pseudotruncus arteriosus indicating the presence of an interventricular communication and maximum obstruction to pulmonary blood flow.

Two of the laboratory features which this patient presents, however, are unusual for typical pseudotruncus arteriosus. One is the electrocardiographic pattern of left axis deviation and counterclockwise rotation of the QRS loop in the frontal plane associated with small R waves over the right precordium. In many ways the ECG might fit better a diagnosis of tricuspid atresia with hypoplastic right ventricle than pseudotruncus arteriosus. In the latter condition the classical feature of elevated right ventricular systolic pressure would make one anticipate a pattern of right ventricular hypertrophy. Aside from tricuspid atresia, endocardial cushion defect (persistent common A V canal) is the other common condition associated with left axis deviation. Virtually all patients with endocardial cushion defect present left axis deviation in the ECG. If this patient were to have an endocardial cushion defect with elevated right ventricular pressure she should manifest right ventricular hypertrophy. Perhaps the precordial leads which lack a pattern of right ventricular hypertrophy indicate hypoplastic right ventricle.

Continuity of the inferior vena cava with the azygos vein is another unusual feature. This condition is commonly present in patients with the polysplenia syndrome. This syndrome is associated with fairly characteristic congenital cardiac malformations and other visceral anomalies. Many of these patients have an endocardial cushion defect. As a group, however, they do not manifest evidence for obstruction to pulmonary blood flow. I would think, however, in view of the continuity of the inferior vena cava with the azygos vein, the ECG, and the clinical picture, that the intracardiac defect is of the endocardial cushion type associated with the hemodynamics of the tetralogy of Fallot. Perhaps slightly supportive evidence for this view is the presence of atrial fibrillation in the ECG. This finding, to me, in congenital heart disease indicates a greatly enlarged atrium which one might anticipate in the face of an endocardial cushion defect. My clinical diagnosis is as follows: polysplenia syndrome with associated visceral anomalies, endocardial cushion defect, tetralogy of Fallot, and perhaps a small right ventricle.

I think the course of the child is unusual and deserves some clinical comment. The child underwent a Blalock-Taussig anastomosis which was of sufficient size as to lead to the development of cardiac failure. Subsequently she developed pulmonary hypertension. Although the elevated pulmonary arterial pressure may have been related to increased pulmonary blood flow, or left sided obstruction, I think it indicates the presence of pulmonary vascular disease. Initially, the cyanosis improved but subsequently she manifested increasing degrees of cyanosis indicating a restriction in the volume of blood flow through the lungs, most likely from changes in the structure of the pulmonary arterial vessels. In my experience, the development of pulmonary vascular disease following a Blalock-Taussig operation is unusual. There are perhaps two explanations for the development of these changes. One is the patient's scoliosis which probably caused restrictive pulmonary disease. It would be helpful to know the P_{CO_2}. I am certain that the impact of scoliosis and resultant reduction in pulmonary volume could have an effect on pulmonary vessels leading to pulmonary vasoconstriction. Certainly, patients with scoliosis may develop pulmonary hypertension and I would think that this process would be accentuated in the face of augmented pulmonary blood flow. The second possibility, though we have no evidence to support it, would be a coexistent condition obstructing pulmonary venous return. Occasionally, tetralogy of Fallot may be associated with mitral stenosis or some other obstructive lesion in the left side of the heart which is not manifested until the patient has sufficient pulmonary blood flow. I think this could be a contributing factor

to development of pulmonary hypertension although it would not be severe since the child did not show a pattern of pulmonary edema

In summary I think the child has the polysplenic syndrome with an endocardial cushion defect and tetralogy of Fallot. The lungs will show occlusive pulmonary vascular disease

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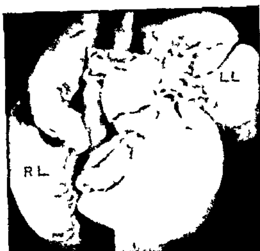


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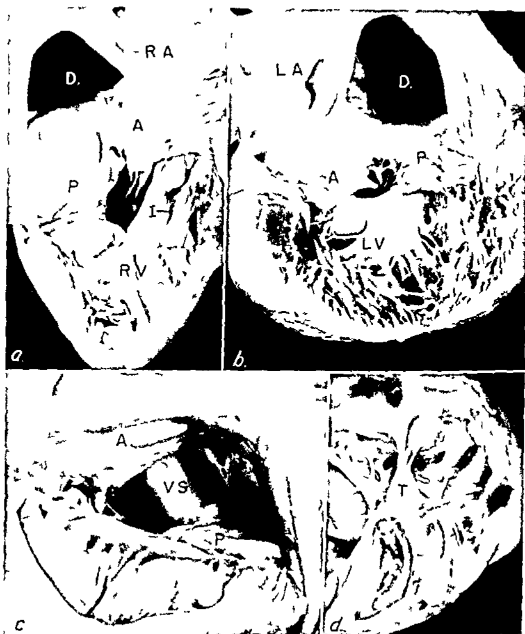


Fig 4 a Right atrium (*RA*) and right ventricle (*RV*) There is a defect (*D*) in the lowermost part of the atrial septum representing a characteristic of persistent common atrioventricular canal Both the anterior mitral and the septal leaflets of the tricuspid valve are cleft yielding a common atrioventricular valve with large anterior (*A*) and posterior (*P*) leaflets The narrow infundibulum (*I*) of the right ventricle is partially shown as well *b* Left atrium (*LA*) and left ventricle (*LV*) The large atrial septal defect (*D*) is apparent as is the common atrioventricular valve The left ventricular lining is highly trabeculated *c* The common atrioventricular valve viewed from above after the atrial septum has been deflected toward the left Beneath the common atrioventricular valve which includes large anterior (*A*) and posterior (*P*) leaflet the crest of the subjacent ventricular septum (*VS*) is apparent *d* Right atrial appendage Although the lining is trabeculated the features are not those characteristic of pectinate muscles Also a focus of organized thrombus (*T*) is present

istinum a small vein bridged the two superior cavae No coronary sinus was present (the usual situation when the left superior vena cava enters the left atrium)

The cardiovascular anomalies observed are summarized in diagrammatic form in Fig 7

There was a functioning Blalock-Taussig anastomosis between the right subclavian and right pulmonary arteries Each major pulmonary artery was markedly dilated and thin walled In addition multiple small atheromas were present in the pulmonary trunk and in the proximal por

tions of each of its main branches In the left pulmonary artery there was an organized embolus represented by a fibrous strand attached to the wall near the junction of the ductus arteriosus The latter was represented by a ligament

Each lung had the fundamental structure of a left lung In addition to the lungs being bilobed in each the pulmonary artery passed superior to a main stem bronchus to hook behind the bronchus of the upper lobe and descend into the lower lobe In addition the distance between the carina and the first division of each main bronchus was the same on the two sides Two pulmonary veins from each lung were identified Each joined the left atrium

Other than the inferior vena cava no abnormal position of the abdominal organs was described The spleen was peculiar in that there was a main globular 340 gram mass and three accessory masses the largest of which was 2 5 cm in diameter The uterus was bicornuate with the left horn larger than the right

Histologic examination of the lungs revealed similar appearances bilaterally The large muscular arteries showed a varying picture Some vessels of this class showed medial hypertrophy while others were thin walled

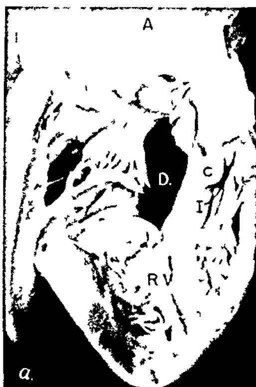
Muscular arteries both small and large focally showed intimal fibrous thickening including degrees wherein severe luminal obstruction resulted (Fig 8) No plexiform or dilatation lesions were observed

DR VAN TASSEL Dr Edwards would you present a closing summary of this interesting case?

DR JESSE E EDWARDS A pivotal point for discussion in this case is the phenomenon of continuity of the inferior vena cava with the azygos vein while the right atrial ostium of the inferior vena cava is the opening of a common hepatic vein This arrangement as observed in this case is highly suggestive perhaps diagnostic of the polysplenic syndrome[1 2]

As far as I am aware the first reported example of continuity of the inferior vena cava with the azygos vein in association with polysplenia was presented by Abernethy in 1793[3]

There are two splenic states each of



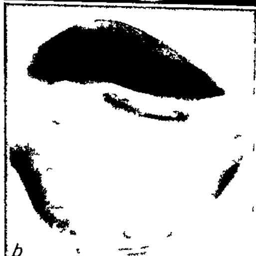


Fig 5 *a* Right ventricle (*RV*) and aorta (*A*) The aorta straddles a large ventricular septal defect (*D*) as it arises from both ventricles The aortic valve is continuous with the anterior leaflet of the common atrioventricular valve The infundibulum (*I*) of the right ventricle is narrow by virtue of a prominent vertical crista (*C*) which contributes to the narrow state of the infundibulum The infundibulum leads to the pulmonary valve which is out of view in this illustration *b* Unopened pulmonary valve from above The valve is bicuspid dome shaped and highly stenotic

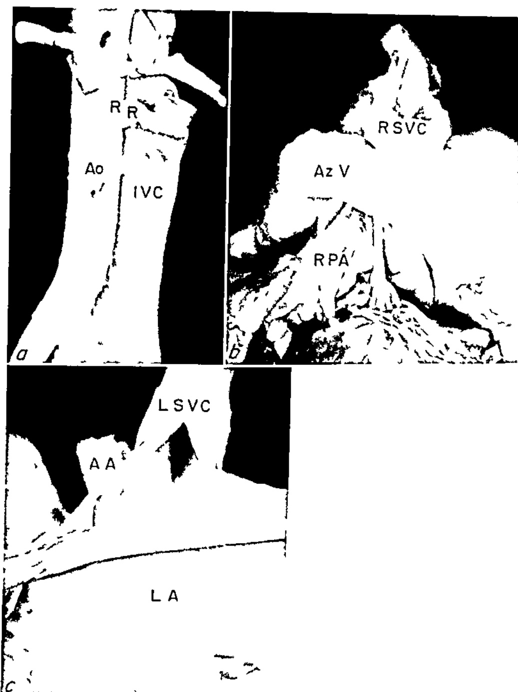


Fig. 6. Systemic veins. *a*, Abdominal portion of aorta (*Ao*) and inferior vena cava (*I V C*). The latter lies in an abnormal position to the left of the aorta. In the upper abdomen above the renal vessels (*R R*, right renal vein) the inferior vena cava deviates toward the right. It became continuous with the azygos vein. *b*, The mediastinal structures viewed from the right showing the large azygos vein (*A V*) which joins the right superior vena cava (*R S V C*). The latter in turn joins the right atrium. The right pulmonary artery (*R P A*) is also in view and shows major dilatation incident to the Blalock-Taussig anastomosis which had been made to this vessel. *c*, Continuity of the left superior vena cava (*L S V C*) with the left atrium (*L A*). The opening lies near the base of the left atrial appendage (*A A*). The hemiazygos vein joins the left superior vena cava.

which tends to be associated with certain types of cardiovascular anomalies. These are the asplenic syndrome and the polysplenic.

The asplenic syndrome has been identified with "bilateral rightsidedness."[4,5] In this each lung possesses three lobes and the intrinsic structure of a right lung.[6] Each atrial appendage resembles a right atrium and sinoatrial nodes are found bilaterally.[7] The two lobes of the liver tend to be of equal size. Abdominal heterotaxia including a right sided stomach and malrotation of the bowel is common.[8]

Cardiovascular anomalies usually include a single atrium with both atrial appendages having the characteristics of the right appendage. The great vessels are usually transposed and a single ventricle is common. There is usually a common atrioventricular valve. Bilateral superior venae cavae are commonly present and frequently the pulmonary veins terminate anomalously in a systemic vein. Pulmonary stenosis is usually present.

The polysplenic syndrome has features which favor a designation of bilateral left sidedness.[9] This, as in the case presented, is represented by bilobed lungs bilaterally. Each atrial appendage tends to have the appearance of a left appendage. In the atrial septum, foramen ovale is usually not identified, suggesting absence of septum II.

In general in polysplenia, the heart is less primitive than in asplenia. Transposition of the great vessels and pulmonary stenosis are usually absent.

Malposition of the organs is common. In a study of 12 cases from our laboratories, Dr. Moller and associates[9] found the following distribution of organ orientations: situs solitus 4 cases, situs inversus 5 cases, and mixed situs 3 cases. The latter designation was used for situations in which the position of certain organs was discordant with the remainder. In the case here discussed, mixed situs may be said to have been present on the basis of a leftsided abdominal inferior vena cava, while the other organs were in normal positions.

The midline apex seen in the current case is common in polysplenia. Union of the left superior vena cava with the left atrium was seen in 4 of Moller's 12 cases, while the presence of a persistent common atrioventricular canal was also seen in 4 of Moller's cases (not necessarily coinciding with union of the left superior vena cava with the left atrium).

While the pulmonary veins terminated normally in the current case, anomalous termination of pulmonary veins to the right atrium is common in polysplenia. In Moller's reported cases, 10 of 12 cases showed such anomalous arrangement (4 total, 6 partial).

The tetralogy of Fallot, as other forms of pulmonary stenosis, is uncommon in association with polysplenia. Nevertheless, the association of the tetralogy with persistent common atrioventricular canal (endocardial cushion defect) is uncommon but not rare.[10] Rao, Anderson, and Edwards[11] observed three such combinations among 85 specimens from patients with the tetralogy of Fallot.

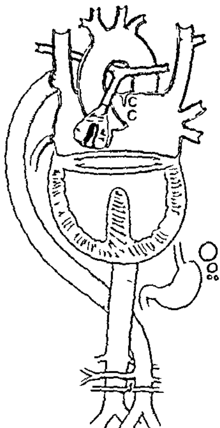


Fig. 7. Summary of cardiovascular anomalies observed.

In general, this association is in a way advantageous in that the pulmonary stenosis of the tetralogy protects the lungs from the effects of the interventricular communication of the endocardial cushion defect. In the case presented, the pulmonary stenosis, particularly at valve level, was severe and represented a dominant lesion as evidenced by the prominence of cyanosis.

Finally, a feature of additional interest was the documented pulmonary hypertension in the presence of the functioning Blalock-Taussig anastomosis. While the



Fig 8 Photomicrograph of intrapulmonary arteries *a* The larger vessel which is a large muscular artery shows a thin wall while the smaller vessel being a muscular arteriole shows intimal fibrous proliferation (Elastic tissue stain ×75) *b* A large muscular artery shows medial hypertrophy and focal intimal proliferation (Elastic tissue stain ×60) *c* A large muscular artery shows irregular medial hypertrophy and moderately severe intimal proliferation (Elastic tissue stain ×60) *d* A large muscular artery shows medial hypertrophy and virtual occlusion of the lumen by nonspecific intimal fibrous proliferation (Elastic tissue stain ×100)

kyphoscoliosis may have contributed to this abnormality, it is probable that the shunt was influential as the important basis for pulmonary hypertension The occlusive pulmonary vascular disease observed at necropsy was of such nature not usually seen in kyphoscoliosis It is our view that these lesions complicated the increased pulmonary flow resulting from the surgical anastomosis

In other patients without skeletal thoracic disease we have observed similar and more severe occlusive pulmonary vascular lesions following creation of a systemic pulmonary anastomosis for congenital pulmonary stenosis [1]

Final diagnosis

The final diagno is was polysplenia with endocardial cushion defect and tetralogy of Fallot

We are indebted to Dr John T El trom for the specimen of the th racic organs and major blood vessels and for the descr ption of the necropsy findings

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Incidence of persistent atrial fibrillation and conduction defects in coronary heart disease

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Coronary heart disease (CHD) has often been regarded as a common etiological factor of atrial fibrillation and conduction defects[1-3] There are however only a few reports which actually give the frequency of such disturbances in large populations of coronary heart disease[4-7]

In order to test this theory, we have studied 916 patients with coronary heart disease during observation periods of from 1 to 17 years In this group of patients we have analyzed the frequency of persistent atrial fibrillation and atrioventricular (A V) and intraventricular conduction defects and have tried to assess their etiology and their prognostic importance

Patient series

The present assemblage of 916 cases comprises patients from two clinical groups (1) 444 patients (214 women and 230 men) with hypercholesterolemia and coronary heart disease either proved myocardial infarction or clear cut effort angina or both and (2) 472 (54 women and 418 men) patients below the age of 51 years with myocardial infarction

For the diagnosis of hypercholesterolemia we required two cholesterol determinations with values above 300 mg per cent and/or the presence of tendinous xanthomas For details of selection and clinical and biochemical assessment reference is made to our earlier study[8] from which patients in the present study were taken The mean age in this group was 67 years (range 35 to 86 years)

Patients with myocardial infarction in early age have been thoroughly described elsewhere and those data represent a follow up study[9] As might be expected, a number of patients in this second group also had hypercholesterolemia However, no patient appears in both groups The mean age at follow up was 50 years (range 28 to 61 years) Fig 1 represents an illustration of the entire patient series (groups 1 and 2) in terms of sex and age and the incidence of atrial fibrillation bundle branch block and A V block

Methods

In most cases the electrocardiogram (ECG) was recorded with a four-channel

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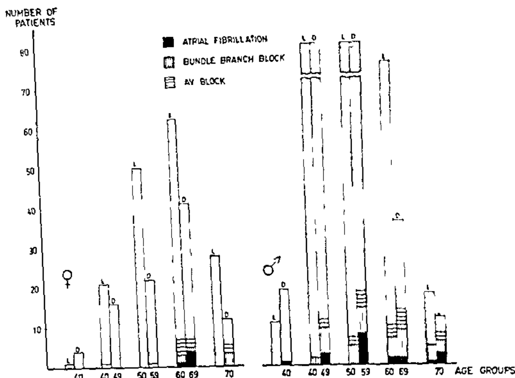


Fig 1 Total patient series according to sex and age with incidence of atrial fibrillation bundle branch block and A V block among living and dead in different age groups ♀ = women ♂ = men L = living patients D = deceased patients

direct writing electrocardiograph Elema No 42 in the first few years of the study only three extremity leads and an IV R lead were used Later four precordial R leads and three unipolar leads (aV_R aV_L and aV_F) were added

Atrial fibrillation was recognized according to the usual criteria—absolutely irregular ventricular complexes together with fibrillation waves at a frequency above 350 per minute Bundle branch block and A V block have been defined according to the Minnesota code [10] Unspecified bundle branch block corresponds to intraventricular block of the Minnesota code

ST T changes indicative of coronary insufficiency and/or of left ventricular strain have not been separated but have been assembled together in one group and labelled as coronary insufficiency Digitalis influenced ST T changes labelled as coronary insufficiency must have occurred in fewer than 1 per cent of the cases

For the ECG diagnosis of myocardial infarction we have required pathological Q and QS complexes and/or abnormal progression of R waves in precordial leads ECGs with changes indicative of both coronary insufficiency and infarction have been assigned to the latter group We were able to reinvestigate the majority of patients in this study In those who could not be reached or had died the final ECG recordings were traced and examined The observation time for each patient was calculated as from the time of original diagnosis to the date of the latest follow up ECG Each instance of ECG abnormality such as atrial fibrillation bundle branch block or A V block was traced back to determine the time of onset and the possible clinical cause Only persistent alterations of at least one week s duration were accepted Among those who died during the time of observation an ECG had been recorded in 52 per cent in the final 2 months of life In 21 per cent an ECG had been taken 2 to 12 months before death and in the remaining 27 per cent an ECG had been made more than 12 months before death In the groups of

Table I. Survival in relation to ECG signs of coronary heart disease for women and men

Variables	Normal		ECG diagnosis						Totals
			Coronary insufficiency		Myocardial infarction suspected		Myocardial infarction proved		
	Women	Men	Women	Men	Women	Men	Women	Men	
Living	71	115	45	42	7	23	35	172	510
Dead	9	18	22	37	9	20	51	147	313
Total	80	133	67	79	16	43	86	319	823

Table II. Survival in relation to atrial fibrillation and conduction defects for women and men

Variables	ECG diagnosis										Totals
	Atrial fibrillation*		Bundle branch block						AV block II + III*		
			Left*		Right		Unspecified				
	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	
Living	1	3	1	4	—	6	1	6	3	5	30
Dead	4	17	4	17	2	8	—	2	3	10	67
Total	5	20	5	21	2	14	1	8	6	15	97

*Two patients with atrial fibrillation and two with AV block also had bundle branch block. These patients are therefore listed twice.

patients who died we have analyzed the heart weight in the autopsied cases. In about 90 per cent of the cases coronary heart disease was the main cause of death.

Results

In Table I the frequency of various ECG signs (normal ECG, coronary insufficiency, suspected myocardial infarction and proved myocardial infarction) have been arranged in relation to survival.

Atrial fibrillation and conduction defects were found in a total of 97 ECG's of 93 patients. Four patients, two men with atrial fibrillation and two with A-V block, also had left bundle branch block.

For the patients with atrial fibrillation and conduction defects, the ratio of women to men was 1 : 4 whereas this ratio was 2 : 5 for the whole study group (Table II).

Below the age of 50, 1 woman out of 42 had such ECG changes; in the 50 to 60 year age group, 1 woman out of 72 had these ECG changes; in the 60 to 70 year age group, 1 woman out of 9 was so affected and in the 70 to 80 year group 1 woman out of 10 exhibited the changes. These results can be compared to those recorded for the men in our patient series: below the age of 50, 1 man out of 19 presented such ECG changes; in the 50 to 60 year age group, 1 man out of 11 had these ECG changes; in the 60 to 70 year age group 1 man out of 6 was so affected, and in the 70 to 80 year group 1 man out of 3 exhibited the changes. These data proved conclusively that men had fibrillation and conduction defects earlier and more frequently than women.

It is apparent from Fig. 1 that there was

Table III Etiologic factors of probable importance in relation to ECG findings

Probable or possible etiology	Atrial fibrillation	Bundle branch block			A V block I
		Left	Right	Unspecified	
Thyrotoxicosis	1 (4)	—	—	—	1‡ (5)
Rheumatic valvular disease	11 (44)	1† (4)	—	—	—
Signs of coronary heart disease (CHD) prior to AF and CD	12 (48)	19 (73)	10 (63)	8 (89)	14 (74)
CHD only	6 (24)	12 (46)	6 (37)	7 (78)	8 (42)
CHD with hypertension	6 (24)	7 (27)	4 (25)	1 (11)	6 (32)
AF and CD prior to signs of CHD	—	5 (19)	3 (19)	—	3 (16)
Unknown if signs of CHD or AF and CD appeared first	1 (4)	1 (4)	3 (19)	1 (11)	1 (5)
Total	25	26	16	9	19

Diagnosis*

T t l se ie 916 p ti t th x pect i nd myocardial infarction ... ce t of ... t gory i pare theses
*Total number of atrial fibrillation (AF) and conduction defect (CD) = 97
† yphilitic valvular disease
‡Rheumatic carditis only

a high mortality rate in the patients with these ECG changes 66 per cent of the women and 65 per cent of the men had died at the end of the observation period as compared to the rate of about 40 per cent for the total study group The highest mortality rate was present in those patients with atrial fibrillation and the lowest rate was observed in those with unspecified bundle branch block these percentages were 84 and 22 respectively

Definite ECG evidence of myocardial infarction was present in cases with atrial fibrillation or with conduction defects in 50 per cent of both women and men the same incidence for both sexes also applies to the whole study group

Possible etiological factors have been listed in Table III Thyrotoxicosis and rheumatic valvular disease are clear-cut etiological factors These factors also apply to a 67 year-old man with left bundle branch block who had syphilitic valvular disease and to a 46 year old woman with A V block which could be traced back to an acute episode of rheumatic fever For the present work we have chosen a high border line for hypertension i e 110 mm Hg diastolic pressure

In 33 of 94 patients the atrial fibrillation or the conduction defect was present before angina pectoris or myocardial infarction was diagnosed As seen in Table III approximately half of the patients with atrial fibrillation had rheumatic valvular disease or thyrotoxicosis

In those patients in whom the probable etiology was CHD (signs of CHD before atrial fibrillation and conduction defect) the average survival time was shorter than for those patients in whom hypertension was an additional etiological factor In the former category many patients died within a few months whereas the survival rate for the latter group was usually several years

Table IV presents the incidence of new cases of atrial fibrillation and conduction defects during the observation time in subgroups of the two parts of the total patient series The extremely low incidence of these abnormalities in the large category of infarctions in early age should be noted This means that there was no further incidence of atrial fibrillation and that only four instances of conduction defects were discovered in 275 persons observed during more than 20 000 patient months (approximately 1 to 17 years) after their first myocardial infarction Another point of interest is the small number of persisting atrial fibrillation and conduction defects as a consequence of acute myocardial infarction (in only 9 out of 61 new cases or 15 per cent)

Table IV New cases of atrial fibrillation and conduction defects during the observation time in terms of clinical groups and number of patients

Clinical groups	No of patients	Total observation time (patient months)	Diagnosis				
			Atrial fibrillation	Bundle branch block			A V block
				Left	Right	Unspecified	
Hypercholesterolemia							
Living							
Angina pectoris	142	9 272	1	—	—	—	2
Myocardial infarction	124	8 489	2 (1)*	1	2	1	2 (1)
Dead	178	6 979	6 (1)	11 (1)	2	—	7 (1)
Young infarctions							
Living	275	20 678	—	—	1 (1)	4	1
Dead	197	5 441	6	4 (1)	3 (2)	2	2
Total	916	50 859	15 (2)	17 (2)	8 (3)	7	14 (2)

*Figures in parentheses indicate the number of cases that acquired fibrillation or block during an episode of acute infarction.

Atrial fibrillation was present in 25 patients or 2 7 per cent of the total patient series Fourteen of the 21 patients who died were autopsied In 10 there were signs of old and/or recent myocardial infarction In 6 of the patients autopsied there was a diffuse fibrosis of large areas of the myocardium and 5 of the 6 had electrocardiographic evidence of myocardial infarction in their final ECG In the one remaining case there was valid clinical evidence of myocardial infarction In these six cases mitral stenosis hypertension or coronary heart disease (in the absence of other factors) were considered as etiological factors

Left bundle branch block was present in 26 patients or 2 8 per cent of the patient series Nine of the 21 patients who died were autopsied All had macroscopic evidence of myocardial infarction and at least two had microscopic evidence of diffuse myocardial fibrosis The etiology in these two cases was CHD with hypertension, or CHD only

Right bundle branch block was present in 16 cases or 1 7 per cent of the patient series Five of the ten patients who died were autopsied In four there was macroscopic evidence of myocardial infarction and in two cases (one with infarction) there was myocardial fibrosis The etiology in the latter two cases was CHD only in one patient and CHD with hypertension in the other

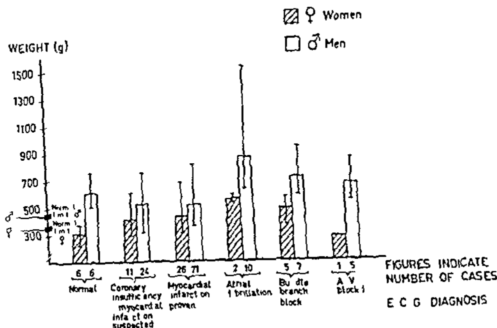
Unspecified bundle branch block was present in 9 cases or 0 98 per cent of the patient series One of the two patients who died was autopsied and presented microscopic evidence of myocardial infarction

First degree A V block was present in 19 patients or 2 1 per cent of the patient series Eight of the 12 patients who died were autopsied In five there was macroscopic evidence of myocardial infarction and in two cases evidence of myocardial fibrosis The etiology in these last two was CHD only in one case and hypertension with CHD in the other No instance of second degree A V block could be found

Third degree A V block was present in two patients (0 2 per cent of the patient series) both of whom were living at the end of the observation time The etiology was CHD only in both patients and in one the total A V block began in connection with an episode of acute infarction No case of Wolff Parkinson White (WPW) syndrome was present in this patient group

Heart weights are presented in Fig 2 From the illustration it can be seen that the patients with fibrillation and conduction defects seem to have larger hearts than the patients with normal ECG s or those pa

I m 84
mb 1



Fi Mean heart wei hts in cases with coronary heart disea e cla ified acc rding to ECG criteria Bars indi cate ranges for men and women

tients with ECG changes characteristic of coronary heart disease Furthermore there seems to be a tendency for larger hearts in patients with fibrillation compared to those having conduction defects No correlation was found between diastolic blood pressure and heart weight The same general trends which hold for heart weights also apply to heart volumes

Discussion

The incidence of atrial fibrillation and conduction defects (bundle branch block and atrioventricular block) in various population studies in studies of coronary heart disease and in our present patient series has been given in Table V The comparison is to some extent invalidated because the criteria for ECG evaluation have by no means been uniform However the code suggested by Blackburn and associates[10] seems to have been increasingly adopted in recent years

The lowest incidence of atrial fibrillation and conduction defects was found as expected among aviators in the U S Air Force[11] The cases in this study were practically all below the age of 50 years

With continuous ECG monitoring in acute myocardial infarction a greater number of rhythm and conduction disturbances have been revealed[12,13] The studies in patient groups with angina pectoris and/or earlier infarctions are comparatively rare but these studies show a lower frequency of such disturbances than in cases of acute infarction[4,15]

In the series of 317 patients with coronary heart disease in a population study of 6 672 adults[6] there was a slightly lower incidence of such ECG changes on the whole as compared to the results for our series The incidence of ECG changes in our study was however lower than the number of such changes found in acute myocardial infarction and in acute myocarditis The highest frequency of rhythm and conduction defects was found in a study group having myotonic dystrophy[16]

From Table VI it is evident that ECG abnormalities as a rule increase with advancing age No conclusions have been made from patients below the age of 40 years and above the age of 70 years because of the limited number in each group These groups have therefore been omitted In order to facilitate a comparison of our material with the Tecumseh study[17] we have presented a sex and age matched correlation of patients (both living and

Table V Per cent incidence of certain ECG findings

Authors and year	*Type of study*	*Diagnosis*					
		Atrial fibrilla tion	*Bundle branch block*		*AV block*		
			Left	*Right*	*I*	*II*	*III*
Population studies							
O trander and associates[17] 1965*	5 129 adults in Tecumseh Mich	0 4	0 35	0 35	1 9	0	0 4
Tibblin[29] 1966*	855 men age 50 years	0 23	0 6	0 7	0 91	0	0
Hiss and Lamb[11] 1962	122 043 men U S Air Force age 16 to 50 years	0 004	0 013	0 18	0 65	0 006	0 00?
Coronary heart disease (CHD)							
Gordon and Garst[4] 1965*	317 CHD patients from population study	0 95	2 4	1 9	—	0 0	0 3?
Shanoff and Little[13] 1965	101 male survivors of infarction Mean observation time 40 months	0	4 0	—	0	0	0
Imperial Carballo and Zimmerman[8] 1960	153 patients during acute infarction	9 8	0	7 8	3 3	3 3	—
Anastassiadis and Sivertson[10] 1961	351 patients during acute infarction	4 7	1 9	4 2	6 3	1 8	? 1
Lick[7] 1963	3 174 cases of recent infarction collected from literature	5 0 to 15 0	—	—	—	1 0 to 1? 0	1 0 to 3 0
Hurwitz and Eliot[8] 1964	500 cases with acute infarction	7 0	-	—	5 0	? 0	2 0
Spann and associates[14] 1964	30 patients with acute infarction (electronic monitoring)	10 0	7 0	7 0	3 0	3 0	0
Bauer Julian and Valentine[12] 1965†	100 patients with acute infarction (electronic monitoring)	16 0	7 0	6 0	—	—	8 0
Dry[13] 1965	126 patients with acute infarction (electronic monitoring)	10 0	6 0			—	3 0
Miscellaneous							
I evander I indgren[31] 1965‡	250 patients with acute myocarditis	7 0 (50)	7 0 (9?)		18 0	5 0 (?7)	4 0 (?3)
Orndahl and associates[16] 1964	29 patients with dystrophic myotonia	20 0	?3 0		28 0		
Present study							
	164 women alive	0 6	0 6	0	1 8	0	0
	104 women dead	3 8	3 8	1 9	2 9	0	0
	377 men alive	0 8	1 1	1 6	0 8	0	0 53
	271 men dead	6 3	6 3	3 0	3 3	0	0
	916 patients (total number)	2 7	2 8	1 7	2 1	0	0 ??

*Cla ified according Blackburn and a ociates (1960)
†Bundle branch block persisted in 3 patie ts
‡Figures in parentheses indicate per cent persistent cl anges after 6 montl s

Table VI. Per cent ECG findings according to age and sex in the Tecumseh[6] and in the present study

Variables	45 to 49 years		50 to 59 years		60 to 69 years	
	Women	Men	Women	Men	Women	Men
Atrial fibrillation						
Tecumseh study	0.1	0	0.9	0	0.5	2.3
Present study						
Living	0	0	0	0	1	7.7
Dead	0	3.0	0	5.6	8.8	4.5
Left bundle branch block						
Tecumseh study	0	0.7	0.6	0.9	0	1.1
Present study						
Living	0	0	0	0.6	1.6	7.7
Dead	0	3.0	0	5.0	7.7	8.1
Right bundle branch block						
Tecumseh study	0	0	0.6	0.3	0.5	1.7
Present study						
Living	0	1.0	0	0.6	0	1.3
Dead	0	3.2	0	1.6	2	4.1
A-V block						
Tecumseh study	0.6	3.5	3.1	1.2	4.1	4.5
Present study						
Living	4.5	0	0	0.6	3	2.7
Dead	0.7	1.0	2.8	3.0	7.6	8.1

dead) in our study group with the patients in that study (see Table VI).

A comparison of our patient series having coronary heart disease with a population study of normal individuals reveals a striking similarity with respect to the incidence of atrial fibrillation and conduction defects. This is especially valid for the most comparable groups of our living patients and those from the Tecumseh study.[6,7] The similarity is somewhat astonishing in view of the fact that our study represents a long term follow-up (more than 50,000 patient months) compared with the "one-shot" survey of Tecumseh. This certainly does not favor the opinion that CHD is a main causative factor for atrial fibrillation and conduction defects. This conclusion is also supported by the observation of only one new case of atrial fibrillation or conduction defects appearing in about 850 patient months (see Table IV). Moreover, it is interesting to mention that only 9 patients out of 774 (1.2 per cent) had persistent disturbances (AF + block) after acute infarctions (atrial fibrillation 0.3 per cent, bundle branch block 0.6 per cent, A-V block 0.3 per cent). In this connection it should be noted that therapeutic measures such as the successful conversion of atrial fibrillation have not been applied in our patient series.

The various possible etiological factors in our study group and in a similar survey from the literature are presented in Table VII. A comparison of the different studies is somewhat difficult because there was no uniform definition of hypertension and coronary heart disease. We started with a patient group having coronary heart disease, whereas other investigators began with a selection of patients with atrial fibrillation and conduction defects. There is a fairly good agreement between our etiological classification for atrial fibrillation and bundle branch block and that of the other studies.

The results from these comparisons do not therefore indicate coronary heart disease to be of such etiological importance for

Table VII. Per cent etiologic distribution in atrial fibrillation and conduction defects

Variables	*Atrial fibrillation*			*Bundle*	
				Left	
	Sokolow and Ball[2] *1956*	*Rokseth and Storstein*[33] *1963*	*Hurst and associates*[34] *1964*	*Johnson and associates*[35] *1951*	*S… et al.*[41]
Thyrotoxicosis	6.0	5.0	4.0	—	—
Rheumatic heart disease	53	55	20	6	8
Hypertension only	12	10	11	40	4
Coronary heart disease (CHD)	21	20	47	35	[illegible]
CHD only	—	—	35	14	31
CHD with hypertension	—	—	12	21	41
Acute myocardial infarction	—	—	—	—	—
Miscellaneous	8	10	18	17	16
Total number	177	274	230	555	98

*Cited from Friedberg and associates[41] 1963.

atrial fibrillation and bundle branch block as has been commonly assumed.

As regards first degree A-V block, there are definite discrepancies between the patient series of Logue and Hanson[18] and our study group regarding possible etiological factors with a higher rate of coronary heart disease appearing in our group. It is difficult, however, to speculate about the reasons for this.

We had only two patients with third degree A-V block and no patients with second degree A-V block. This very low frequency does not seem to point to coronary heart disease as an important etiological factor for second- and third-degree A-V block, although higher frequencies are reported by others (see Table VII).

It is a time-honored observation that patients with atrial fibrillation seldom develop coronary heart disease.[19, 20] The experience gained from our study seems to make the inverse hypothesis possible, namely, that coronary heart disease fairly seldom leads to atrial fibrillation and that coronary heart disease is an uncommon etiologic factor of atrial fibrillation (1.3 per cent in our study group). Analogous to this, Holzmann[19] only found 5 instances of atrial fibrillation in 500 patients with angina pectoris.

Atrial fibrillation does not always imply histological evidence of atrial damage, since Soderstrom[1] did not find a strong correla tion between these two conditions in 40 patients of histologically proved atrial in farction. However, James, in a detailed anatomical study of the atrial blood supply in 11 cases of acute myocardial infarctio with atrial rhythm disturbances found a coronary occlusion proximal to the origir of the sinus node artery and signs of infarc tion in the sinus node area. In a case of idiopathic atrial fibrillation of twenty years duration, Cancella and Nicolaus[43] describec an occlusion of the sinus node artery. Va nauskas[4], however, found no sinus node artery changes on coronary angiography i some cases of atrial fibrillation of this typ Thus there is still a great deal of contro versy as to the vascular origin of atria fibrillation.

Anatomically, even minor changes in volving a small area of the myocardium containing Purkinje fibers might give ri to an interruption of the specialized con duction pathways with resulting conduc tion defects. Therefore, it should *a priori* b expected that coronary heart disease wit even small infarctions was a frequent cau of bundle branch block. This, however, ha not been proved. The reason for this migh

Right	A-V block					
	First degree	Third degree				
...en ... and ...ates 1950	Logue and Hanson 1944	Penton and associates 1956	Rowe and White 1958	Cud... and associates 1963	Friedberg and associates 1964
—	—	—	—	—	—
8	28	8	8	10	(
20	1	25		8	5
31	14	43	73	37	60
—	—	21	35	12	38
—	—	-	24	—	10
—	—	19	11	25	1
38	57	24	19	45	29
281	100	251	278	130	100

be twofold. First, it is known that the ventricular septum has a very rich blood supply with septal branches from both the left and the right coronary artery.[26] This is the basis for the high degree of potential collateral channels which can secure blood flow even in cases with extensive luminal changes. Second, recent electrophysiological studies[8] seem to indicate that Purkinje fibers actually are more resistant to hypoxia than ordinary myocardium. It may therefore not be surprising to find a rather low frequency of conduction defects in the present study group of selected patients with coronary heart disease.

A striking feature in the autopsied cases was the high incidence of diffuse myocardial fibrosis. This finding was present in 50 per cent of the cases, both isolated and in conjunction with myocardial *infarction*. The question therefore arises if diffuse myocardial fibrosis might be *of specific importance* for the development of atrial fibrillation or conduction defects. It may be worthwhile to investigate this problem further with more refined anatomical *techniques*.

Another important observation was the marked correlation between heart weight and volume and the incidence of atrial fibrillation. In the present *patient* series most cases of atrial fibrillation occurred in patients with a heart weight of 550 Gm. or a heart volume above 600 ml. per square meter of body surface area. This is in agreement with electrophysiologic studies on smooth muscle and atrial strip preparations in which electrical activity was directly proportional to external tension.[27,28]

In the present study it was rather striking that atrial fibrillation or conduction defects develop at a late stage of CHD, namely, a few months to two years before death. However, there is a better prognosis in atrial fibrillation due to thyrotoxicosis, rheumatic heart disease, and myotonic dystrophy.

Summary

Permanent atrial fibrillation and conduction defects (bundle branch block and A-V block classified according to Blackburn and associates[10]) have been studied in a patient series of 916 patients with coronary heart disease.

The following results were obtained:

Incidence. The frequency of atrial fibrillation, left and right bundle branch block, and first-degree A-V block was about 2 per cent. A sex- and age-matched correlation of the incidence of these disturbances *in our* study group with a population study showed astonishing similarities. *Further*

more, there was a very low rate of new cases of atrial fibrillation and conduction defects in our patients (1 new case for 70 patient years). Moreover, only 0.3 per cent of these disturbances persisted after an episode of acute myocardial infarction.

Mortality and prognosis. The mortality rate for patients with atrial fibrillation and conduction defects was nearly twice as high as that of the whole study group. The death rate was especially high for patients with atrial fibrillation and left bundle branch block. The average survival time varied from a few months to two years for most patients with atrial fibrillation, bundle branch block, and first degree A-V block when the probable etiology was coronary heart disease.

Etiology. The analysis of possible etiological factors in the present study of atrial fibrillation and bundle branch block showed approximately the same distribution and frequency compared to other studies of large patient series in the literature.

The result of this study does not support the widespread opinion that coronary heart disease is the predominant cause of atrial fibrillation and conduction defects, because this outcome was seldom found and rarely developed in our follow-up study of 916 patients with coronary heart disease. Future studies should therefore be directed to look for alternative etiological factors.

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Appraisal and reappraisal of cardiac therapy

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The medical treatment of angina pectoris
II. Design of an antianginal drug study

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The evaluation of an antianginal drug is very difficult for many reasons Spontaneous remission or exacerbation of angina may occur Placebo may cause improvement of exercise performance as well as relief of pain [1] Chest pain due to other coexisting disorders may be interpreted as angina Changes in the weather in emotional stress, in the amount of activity, in smoking in dietary habits, and in concomitant medications are some of the many factors that influence the subjective symptom of anginal pain

The design of the exercise study used to evaluate an antianginal drug may also prejudice the results Some of my objections to one such study[2] include the following This exercise study was not double blind Exercise was performed by the patients ascending and descending a two step staircase instead of with a constant load bicycle ergometer which would be associated with a more uniform and reproducible work load The author states that After a light breakfast and at a variable interval following the administration of placebo the patient was exercised until he reported the onset of typical anginal pain ' As angina is precipitated more readily after exercise in the postprandial state [3] the investigator's patients[2] would be expected to have a decrease in exercise performance after placebo compared to active drug Thirty minutes after the first exercise study, active drug was given to all 28 patients on the 3 days they were tested The first 12 patients received a fixed order of drug administration with isosorbide dinitrate on day 1 propranolol on day 2 and isosorbide dinitrate plus propranolol on day 3 This fixed order of drug administration favors the combination of propranolol plus isosorbide dinitrate since a better exercise performance may result on the third day because of training The second exercise test on each day occurred after the administration of active drug and was performed in some patients at a time when the improved exercise performance might be due to the warm up phenomenon [4]

With these variables in mind, the following discussion suggests an approach to the problem of how to design a reliable antianginal drug study

An adequate number of patients (at least 20) with at least 5 episodes of classic

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xertional angina pectoris per week for at east 3 months due to coronary artery dis ase should be evaluated on an outpatient basis Patients with a classical history of xertional angina pectoris and ischemic S-T segment depression of at least 1 mm on the postexercise electrocardiogram (ECG) may be considered as quite likely to have oronary artery disease However the presence of a documented myocardial in farction at least 6 months old or the visuali zation of significant coronary artery dis ease by coronary angiography better docu ment the presence of coronary artery dis ease These patients should be cooperative and able to keep a detailed diary of their anginal episodes and the relationship of these attacks to various precipitating fac tors Patients with chest pain due to other conditions such as diaphragmatic hernia esophagitis peptic ulcer cervical arthritis gallbladder disease and musculoskeletal disorders should be excluded Patients with a marked psychogenic overlay of anxiety who construe every minor ache or chest pain as an anginal attack should be ex cluded Patients in whom there is a sudden increase in severity and frequency of their angina should be excluded Patients with other forms of heart disease uncompen sated congestive failure uncontrolled hy pertension or coexisting disorders that may require hospitalization or change in drug therapy should be excluded

Because of unconscious observer bias an antianginal drug study must be at least double blind If one is evaluating a drug such as propranolol which slows the heart rat making it easy for the investigator to detect whether the patient is on active drug or on placebo other precautions must be taken[5,6] In such a study[5,6] the patients may be followed by cardiac residents in a cardiac clinic The resting and postexercise ECG s may be taken during the exercise studies by cardiac residents without the investigators knowing what the heart rates were until after the entire study has been completed

Some investigators object to a fixed dose double blind crossover study because the active drug is not titrated to meet the patients needs In addition an initial period of improvement lasting during the first 11 weeks on the average may occur in an antianginal drug study and this is attributed to the psychotherapeutic effect of increased attention and care inherent in a research program[7] Therefore the following protocol is suggested

During the first 4 weeks of the anti anginal drug study the patients should be placed on placebo and an exercise study should be performed on each patient during each week During weeks 5 through 8 the patients should be placed on different doses of the active drug each week and an exer cise study performed each week During weeks 9 through 12 the patients should again be placed on placebo In week 13 a double blind crossover study should begin with the dose of active drug being selected on the basis of the exercise studies per formed during weeks 5 through 8 The medications should be coded and placebo or drug should be assigned randomly to the patients using a table of random numbers The same number of placebo and active drug tablets should be given and the placebo should be identical in shape color size and taste to the active drug After 6 weeks of either drug or placebo there should be a washout period of at least 1 week during which the patients should be placed on placebo then the patients who received active drug during the first 6 weeks of the double blind crossover study should receive placebo for 6 weeks and the patients who initially received placebo should receive active drug for 6 weeks Exercise studies should be performed at least 4 times during the last week of the drug and placebo study periods Appro priate laboratory tests should be obtained during the control drug and placebo per iods to determine whether the drug pro duces any toxic effects

During the entire study each patient should keep a detailed diary of every angi nal episode that occurs and its relationship to precipitating factors Dietary and smok ing habits should remain relatively con stant No other antianginal medication with the exception of nitroglycerin should be taken during the entire drug study No change in any medication during the dou ble blind crossover study should be made unless absolutely necessary Tablet counts

should be made after the medication is returned to determine how much medication has actually been taken

Exercise studies should be performed at a time after medication when the medication is expected to exert its maximum effect. Exercise studies should be performed at least 3 hours after a light meal, at the same time of day and at the same time after the administration of medication during the drug period as during the placebo period and in a room with constant temperature that is neither cold nor hot. We prefer to exercise subjects while they are in an upright position on a constant load bicycle ergometer until the onset of angina. Redwood and his associates[8] have shown that it is preferable to choose a progressive work load in the control period so that angina will be produced after 3 to 6 minutes of upright exercise. This same work load should be used in the drug period and in the placebo period. Patients should not smoke or take nitroglycerin for at least 2 hours prior to the exercise studies. Patients should be observed taking their medication prior to the exercise studies. Blood pressures and heart rates should be obtained with the patients sitting upright on the bicycle ergometer at rest and immediately after the onset of angina pectoris. ECG s should be taken prior to exercise, during exercise, and after the onset of angina pectoris

Finally, the data obtained during the double blind crossover study should be statistically analyzed for each individual patient to see if the active drug caused at least a 50 per cent reduction in anginal episodes, caused a significant improvement in exercise performance, caused a significant improvement in ischemic S T segment depression in the resting, exercise, or post exercise ECG s or caused a significant increase in the product of systolic blood pressure and heart rate at the onset of angina compared to the placebo. The incidence and severity of any side effects and any abnormal laboratory data should be tabulated for the active drug and for the placebo. If patients drop out of the study the reasons for their doing so should be thoroughly evaluated

If the data statistically show that the active drug is an effective antianginal agent, and if these data are confirmed by other well-designed studies then a large scale multihospital cooperative study should be conceived and executed to determine whether this medication will have an effect on longevity and on the incidence of myocardial infarction

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Annotations

Hazards of central venous pressure monitoring Pericardial tamponade

Local adverse effects such as thrombosis and embolus, suppurative thrombophlebitis, bacteremia, venous necrosis, and venous laceration secondary to central venous pressure monitoring have been widely reported. Hemothorax, pneumothorax, subcutaneous emphysema, brachial plexus injury, and air emboli have resulted from subclavian vein puncture from central venous pressure (CVP) catheter placement.[1-4] Shearing of the catheter during placement has caused embolization of catheter fragments.[4]

Cardiac perforation with pericardial tamponade has only recently been recorded with death occurring in four of the five reported cases.[5,6] The alarming factor is that three of the five cases were reported in two separate papers from the same institution.[5,6] The diagnosis was readily made in the last of the three patients reported only because this entity had previously been recognized by the thoracic surgeons called in consultation by the attending physicians. This is alarming because the commonly accepted standard for catheter placement and management are exactly the same as those practiced everywhere in the United States. The possibility of death from CVP monitoring itself rather than from the condition for which it is employed must always be considered. It seems probable that some of the hazards of CVP monitoring have been ignored because they have not been recognized.

By placing the catheter using absolutely sterile surgical techniques and applying an antibiotic ointment daily to the insertion site, local infection with subsequent generalized sepsis can be avoided. No medication and only a minimal amount of fluid is infused through the catheter to reduce local and cardiac irritation. The hypovolemic patient is placed in the Trendelenburg position to prevent air embolism. The potential pulmonary complication of subclavicular insertion can be avoided by placement of the catheter in the left median basalic vein.

To minimize the possibility of pericardial tamponade a radiopaque catheter is always used and the catheter tip is never beveled. The exact location of the radiopaque catheter is confirmed by chest film after placement is estimated by external measurement. The catheter tip is not advanced into the right atrium. The catheter is securely sutured and taped to prevent advancement.

Cardiac tamponade can occur shortly after placement or may take 24 to 48 hours before it occurs; however, the longer the catheter is left in the patient the greater the risk and the greater the incidence of all complications.

Pericardial tamponade secondary to the CVP catheter may be rare, but it is extremely serious when it occurs. Where rapid deterioration is noted in any patient with a CVP catheter in place, confirmation of the position of the catheter tip radiographically is mandatory. If there are any signs radiographically or clinically of pericardial tamponade, pericardiocentesis may be therapeutic as well as diagnostic.

It is axiomatic that the physician must always consider the benefits and hazards of any form of management of the patient whether it be diagnostic, therapeutic, or surveillance. He must continuously be aware of all the known and possible complications of his endeavors. This is particularly true of CVP monitoring where the hazards, if they go unrecognized, greatly outweigh the benefits.

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Use of indicator dilution techniques to determine patency of internal mammary artery implants

Since its introduction more than a generation ago the use of dye dilution techniques for the determination of cardiac output and the detection of shunts in the study of the circulation is now a refined and accepted technique.[1,2] The appearance of indicator at a sampling site occurs even with very small shunts from other areas and in addition may be detected in very small concentrations.

The techniques for determining the contribution of internal mammary artery implants to myocardial perfusion and for making an assessment of the value of the operation are well documented.[3-6] The standard technique for the determination of patency and its contribution to myocardial perfusion is internal mammary arteriography. Some question of the validity of arteriographic evidence of collateral flow has arisen and direct electromagnetic flowmeter determinations of flows have shown only a very small flow through the implant in spite of arteriographic evidence of an excellent surgical result.

The following study was undertaken at the time of internal mammary arteriography as a means of substantiating flow from the implant to the myocardium and in particular to determine if any collateral flow existed when the arteriographic evidence suggested an unsatisfactory result.

Methods

Six Caucasian male patients ranging in age from 46 to 57 years with predominantly anterior descending coronary artery disease were studied 16 to 74 months after a left internal mammary pedicle implant. Internal mammary arteriography was performed from a left brachial artery approach using a Sones or Judkins catheter and a 60 per cent Renografin solution for contrast material while recording on 35 mm. cineangiographic film at 60 frames per second.

Indicator dilution curves were inscribed by injecting 10 mg. of indocyanine green dye into the implant and sampling from the coronary sinus by use of a No. 7 NIH catheter. Curves were inscribed in duplicate fashion following which the internal



Fig. 1. Internal mammary arteriogram showing a patent internal mammary artery with filling of the anterior descending coronary artery, a myocardial blush, and early venous phase.

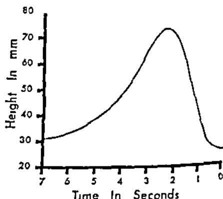


Fig. 2. Indicator dilution curve typical of patients with patent internal mammary artery with filling of anterior descending coronary artery and a venous phase.

Table I *Patients studied by means of internal mammary arteriography and dye dilution injections*

Patient	Coronary lesion	Interval between surgery and study	Implant function	Appearance time	Type of curve	Clinical state
L. M	Total obstruction middle 1/3 of ADCA*	22 months	Patent with filling of distal ADCA and venous phase	Immediate	Sharp deflection	No improvement
C. K	Total obstruction middle 1/3 of ADCA	22 months	Patent to pericardium with collaterals into pericardium and chest wall None to myocardium	6 sec.	Small dispersed	Slight improvement
D B	50% obstruction ADCA at origin from LMCA and 75% obstruction at origin of CCA	23 months	Patent with filling of ADCA with venous phase	Immediate	Sharp deflection	Marked improvement
J F	Total obstruction proximal ADCA with distal collaterals and some disease CCA	16 months	IMA occluded halfway to myocardium	8 sec.	Small dispersed	Moderate improvement
E. B	Total obstruction ADCA in middle 1/3	19 months	Patent with collaterals into ADCA and a venous phase	Immediate	Sharp deflection	Marked improvement
O P	75% obstruction ADCA at origin from LMCA	24 months	Patent into myocardium but no collaterals seen	Immediate	Small dispersed	No improvement

*Abbreviations ADCA = Anterior descending coronary artery CCA = Circumflex coronary artery LMCA = Left main coronary artery

mammary catheter tip was withdrawn just distal to the internal mammary orifice and a control curve was recorded

Indicator-dilution curves were inscribed using a Waters densitometer a Harvard withdrawal pump and a Texas Instrument recorder Lag time of the sampling system was determined by the length of time necessary for blood to appear at the densitometer site

Results

Table I presents a tabulation of the patients studied with the type of coronary lesion present the interval between implantation and study the arteriographic results the appearance time of the indocyanine green indicator in the coronary sinus a description of the curve and the clinical results No correlation could be made between the clinical state and the presence or absence of patency

The three patients with obvious filling of the anterior descending coronary artery and a venous phase in the coronary sinus (Fig 1) had immediate appearance of indocyanine green indicator in the coronary sinus with a sharp deflection (Fig 2) One patient with an implant patent into the myocardium but with no evidence of collateral flow myocardial blush or venous phase had instant appearance of indicator with a small dispersed curve (Fig 3) Two patients with implants clearly not functioning into the myocardium had small dispersed curves delayed 6 and 8 seconds after injection of indicator with curves similar to those obtained with controls who were injected in the left subclavian artery (Fig 4) Indicator appearance time for the controls ranged from 6 to 9 seconds

Discussion

Indicator-dilution curves utilizing indocyanine green dye were explored in determining the patency of internal mammary artery implants Detection techniques for this dye are very sensitive and any indicator material detected in the coronary sinus after injection into an internal mammary artery implant would signify collateral flow from the in-

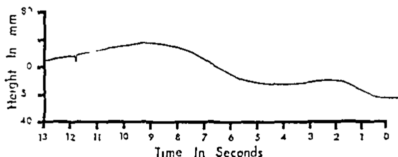


Fig 3 Indicator dilution curve in a patient with a patent implant into the myocardium but without other evidence of collateralization

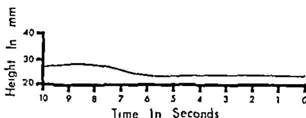


Fig 4 Indicator dilution curve typical of patients with an occluded internal mammary artery prior to entering the myocardium

ternal mammary artery implant into the coronary circulation

Three patients with high grade arteriograms with filling of the anterior descending coronary artery and a venous phase had instant appearance of indocyanine green indicator in the coronary sinus with a sharp curve inscribed whereas two patients without evidence of patency of the internal mammary artery implant to the myocardium showed dye dilution curves consistent with systemic circulation only

One patient showed evidence of some myocardial perfusion despite the fact that arteriographically no venous phase or collateral flow could be detected even though the implant was patent into the myocardium

Summary

Indicator dilution indocyanine green dye curves were inscribed by injecting into the internal mammary artery and sampling from the coronary sinus in six patients being studied postoperatively after left internal mammary artery implants The results were predictable from the internal mammary arteriograms patients with obvious collateral flow on arteriography had immediate appearance of indocyanine green indicator in the coronary sinus and patients with occluded implants prior to entering the myocardium had only systemic circulation of indocyanine green One patient with a patent vessel into the myocardium but with no evidence of collateral flow had an early but dispersed curve indicating that some myocardial perfusion was occurring if the implant remained patent but whose arteriograms otherwise pointed to a poor result.

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Acute elemental phosphorus poisoning in man

Cardiovascular toxicity

The mortality rate after ingestion of yellow phosphorus ranges from 30 to 50 per cent.[1-4] Most deaths occur within 36 hours, reportedly secondary to peripheral vascular collapse, cardiac arrest, and cardiac failure. Despite the frequency of shock in phosphorus poisoning, we are unaware of any previous hemodynamic or chemical studies clarifying its pathophysiology. We have recently evaluated the cardiovascular function of a 16-year-old girl who ingested 1100 mg. of elemental phosphorus in a suicide attempt.

Peripheral pulses were palpable at a rate of 110 per minute. Blood pressure by palpation was 60 mm. Hg systolic. The skin was cold, nail beds were cyanotic, and capillary filling was poor. Respirations were 40 per minute; the lungs were clear to auscultation. There was no palpable point of maximal impulse (PMI); heart sounds were distant with an audible third heart sound and a single second heart sound. The electrocardiogram (ECG) revealed atrial fibrillation with wide, slurred QRS complexes. A supine chest x-ray demonstrated diffuse cardiac enlargement and clear lung fields. One hundred per cent oxygen was administered by nasotracheal tube and the pH was raised to 7.3[illegible] with intravenous sodium bicarbonate and maintained at or above this level with periodic sodium bicarbonate infusion. Serum electrolytes after pH improvement were normal except for carbon dioxide 9.0 mEq. per liter and potassium 3.0 mEq. per liter. Blood sugar was 486 mg. per 100 ml.

Results of the shock evaluation are summarized in Fig. 1. On 0.03 μg per kilogram per minute of isoproterenol, the mean arterial pressure was 37 mm. Hg and the central venous pressure 17 mm. Hg. With discontinuation of the isoproterenol and acid-base balance improvement, the mean arterial pressure rose to 47 mm. Hg. Urine production began concurrently with dopamine infusion; however, the mean arterial pressure fell to 35 mm. Hg. Levoarterenol infusion at a rate of 0.13 μg per kilogram per minute increased the mean arterial pressure to 46 mm. Hg and urine production continued. Despite the low blood pressure, the patient was able to answer questions and respond to commands, although she was lethargic. All indocyanine green dye curves revealed a late appearance time with an initial low peak followed by a higher peak and a prolonged flattened disappearance.

At 5:30 A.M. a right heart catheterization was performed to clarify the hemodynamic problem. All chambers of the heart were entered, the left atrium and left ventricle being entered through the patent foramen ovale. Pressures revealed a right atrial mean of 16 mm. Hg, a right ventricle pressure of 24/16 mm. Hg, a pulmonary artery pressure of 24/17 mm. Hg, a left atrial mean pressure of 20 mm. Hg, a left ventricle pressure of 68/21 mm. Hg and femoral artery pressure of 74/30 mm. Hg. Hand injections of 10 ml. of contrast material into each ventricle revealed a markedly generalized decrease in contractility. Indocyanine green dye curves and oxygen saturations revealed bidirectional shunting at the atrial level with a pulmonary-to-systemic flow ratio of 1.5 : 1.0. Systemic cardiac output was calculated from the left atrial to the femoral artery dye curve after assuming a linear semilog plot of the downslope and was 5 L. per minute. Calculations revealed markedly diminished systemic and pulmonary resistances of 433 and 714 dynes/sec./cm.[illegible], respectively. Clinical condition, blood pressure, and urine production remained unchanged until 1:00 P.M. when, [illegible] hours after ingesting the yellow phosphorus, cardiac standstill occurred and the patient could not be resuscitated.

At postmortem examination the heart was pale, dilated, and weighed 300 grams. The coronary arteries and valvular structures were unremarkable. The foramen ovale was patent. Microscopic sections revealed diffuse changes throughout the myocardium with the myocardial cells separated by interstitial edema without cellular infiltrate. The cytoplasm was vacuolated with pale linear areas.

Elemental phosphorus was administered to Sprague-Dawley rats in an effort to elicit a direct toxic biochemical effect on the myocardium. Methods previously applied for the study of the toxic effect of emetine hydrochloride and certain antiarrhythmic agents were used to evaluate amino acid incorporation into soluble myocardial proteins and actomyosin.[illegible]

Depression of tritiated leucine incorporation into the pooled soluble cardiac proteins and actomyosin of the experimental animals was noted. Comparison between the specific activity of protein isolates from the control group and from experimental hearts revealed a 24 to 40 per cent inhibition of leucine incorporation produced by administration of phosphorus.

The hemodynamic data obtained from our patient strongly suggest a direct toxic effect upon the myocardium and the peripheral vessels. Vascular damage was evidenced by the extremely low systemic resistance (despite the low blood pressure) and the failure of powerful alpha adrenergic agents to increase the resistance substantially. The myocardial effect was evidenced by the elevated ventricular end diastolic pressures, the abnormal pressure tracings obtained in both ventricles, the extremely poor contractions noted on angiography, and the generalized cardiac dilatation which apparently led to opening of the foramen ovale allowing bidirectional shunting at the atrial level. Additional evidence of myocardial dysfunction was the very low left ven-

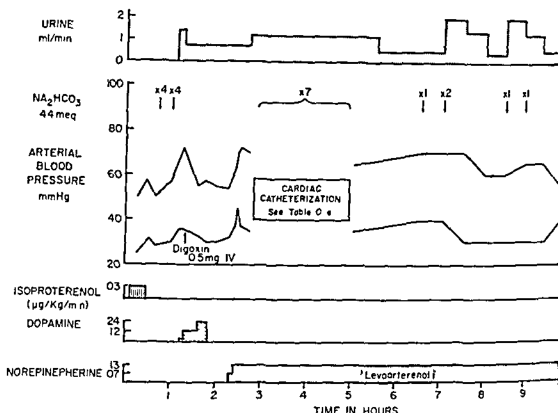


Fig 1 Hospital course of a 16 year old girl who ingested 1100 mg of elemental phosphorus nine hours prior to the recording of the initial values Femoral artery pressures and urine flow are shown as well as the various drugs used in an attempt to correct the cardiovascular abnormalities See text

tricular pressure rise (dp/dt = 588 mm Hg per second) in the presence of a high preload [6,7]

Most toxicological references merely state that elemental phosphorus acts as a general protoplasmic poison probably in interfering with enzyme systems [8] However Barker and co-workers[9] found phosphorus to depress intracellular protein synthesis in the liver but not in the pancreas or duodenum Our data indicate a similar depression of rat myocardial protein synthesis due to acute phosphorus poisoning Although we are unable to determine the mechanism by which phosphorus acts to inhibit amino acid incorporation into myocardial proteins we feel that the metabolic effect demonstrated is related to the cardiac dysfunction seen in our patient

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Volume 84
Number 1

Angle of traction of the papillary muscle in normal and dilated hearts A theoretic analysis of its importance in mitral valve dynamics

The left ventricular papillary muscles are important constituents of the mitral valve apparatus. During ventricular systole the papillary muscles necessarily develop tension to prevent the mitral valve from everting into the left atrium, thereby preventing regurgitation of blood from the left ventricle.[1]

The force developed by the left ventricle and exerted against the mitral leaflets guarding the atrioventricular orifice is directly proportional to the area of the orifice In a previous report the large force exerted against the mitral leaflets and supported by the papillary muscles in both normal and dilated hearts was described[2] In the following discussion the importance of the changing angle of traction of the papillary muscles with respect to the efficiency of papillary muscle function as systole progresses is emphasized.

The force (F) in dynes exerted on the mitral valve leaflets is given by the formula

$$F = P \times A \times 1{,}333.2$$

where P equals ventricular pressure (mm Hg) and A equals the area (sq cm.) of the mitral valve orifice. The force exerted on the mitral valve leaflets is supported by the papillary muscles and the annulus of the mitral valve orifice with a precision that keeps the mitral valve orifice sealed throughout systole

From examination of many hearts at necropsy it is evident that in the relaxed state the papillary muscles normally occupy a position along the ventricular wall that is approximately one half the distance from the apex of the left ventricle to the mitral valve annulus. If for convenience one assumes the ventricle to be spherical the angle formed between the papillary muscles and the mitral valve orifice at the point of attachment of the papillary muscles to the edges of the mitral valve leaflets (angle α) during early systole is about 45 (Fig 1) However during ventricular ejection the volume and therefore the radius of the normal size left ventricle progressively reduces markedly Also the papillary muscles and chordae tendineae progressively migrate centripetally during systole to a position almost perpendicular to the mitral valve orifice so as to form almost a 90° angle between the mitral valve orifice and the attachments of the papillary muscles to the edges of the mitral valve leaflets (Fig 1)

The importance of the progressive change in the angle of traction of the papillary muscles as systole progresses can be illustrated by the following theoretic considerations If it is assumed that a normal size ventricle with a mitral valve orifice of 8 sq cm. contains 95 c.c. of blood at the end of diastole the force (F) exerted on the mitral valve during early systole (intraventricular pressure 80 mm Hg) would be 8.53×10^5 dynes. If one assumes that the annulus and ventricular wall support one half of the total force then each papillary muscle would have to support one fourth of the total force or 2.13×10^5 dynes However to support this force the papillary muscle would have to provide an even greater counterforce, since its force is applied to the orifice at an angle less than 90° Thus with an angle of traction of 45 a papillary muscle would have to develop a force of 3.01×10^5 dynes in order to exert the necessary force of 2.13×10^5 dynes on the mitral valve leaflets Following ejection of 85 c.c. of blood and assuming an intraventricular pressure of 100 mm Hg at the end of systole and no change in the size of the mitral valve orifice of 8 sq cm the total force exerted on the mitral valve at the end of systole would be 10.67×10^5 dynes. However since the angle of traction is almost 90° at that time during the cardiac cycle (Fig 1) the force required of a single papillary muscle to support its share of the force against the mitral valve would be reduced to 2.68×10^5 dynes Thus although the intraventricular pressure and in turn total force on the mitral valve leaflets are increased at the end of systole the force required of the papillary muscles to support the mitral valve leaflets is much less because of their increased mechanical advantage due to the change in the angle of traction from 45 to almost 90° when the ventricle is contracted and essentially empty The decrease in force or tension required of the papillary muscles occurs parabolically Differences of plus or minus 10 from an angle of traction of 90° are of little consequence

Unfortunately with ventricular dilatation the mechanical advantage of the papillary muscles of the normal size heart during the late phase of ventricular systole is lost. In the dilated heart the papillary muscles are displaced centrifugally and are situated relatively closer to the orifice of the mitral valve than in the normal size heart Such a position causes the papillary muscle to have an angle of traction with the mitral valve leaflets which could approximate 30° If such a dilated left ventricle contained 500 c.c of blood and if the mitral valve orifice increased to 13 sq cm. (intraventricular pressure of 80 mm Hg) the total force on the mitral

I these calculations we assume an arterial blood pressure of 1?0/80

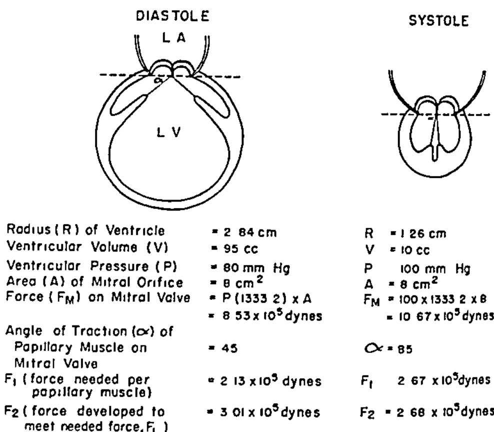


Fig. 1 Diagram showing the influence of the time course of spatial orientation of papillary muscles of the mitral valve during systole in the normal size heart on papillary muscle efficiency Consult text for details

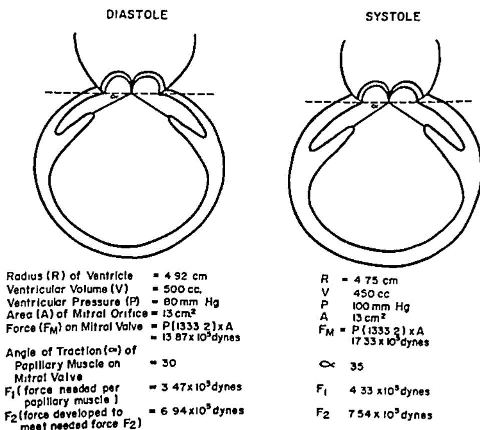
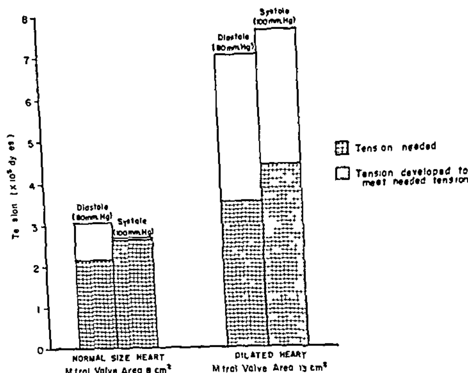


Fig 2 Diagram showing the influence of the time course of spatial orientation of papillary muscles of the mitral valve during systole in the dilated heart on papillary muscle efficiency Consult text for details



Fi 3 The influence of heart size on force needed of and developed by a left ventricular papillary muscle

valve during early systole would be 13 87 × 10⁵ dynes (Fig 2) and the total force supported by each papil lary muscle would be 3 47 × 10⁵ dynes With an angle of tra tion of 30 the total force required of each papillary muscle to provide an effective force of 3 47 × 10⁵ dynes would be 6 94 × 10⁵ dynes Even with a stroke volume of 50 c c the radius of the dilated ventricle would decrease very little (Fig 2) and thus the angle of traction of the papillary mus cle would remain essentially unchanged perhaps increasing to 35 in some hearts Therefore with an intraventricular pressure of 100 mm Hg at the end of systole and a mitral valve orifice of 13 sq cm the total force on the mitral valve would be 17 33 × 10⁵ dynes and an effective force of 4 33 × 10⁵ dynes would be required of each pap llary muscle How ever because the papillary muscle migrated only slightly (to a traction angle of about 35) the force required of the papillary muscle to produce the force of 4 33 × 10⁵ dynes would be 7 54 × 10⁵ dynes This is an increase in force rather than a marked decrease as seen in the normal size heart. If th angle of tract on of the papillary muscle in the d lated heart could have increased to almost 90° near the end of systole as occurs in the normal size heart the force required of a single papillary muscle would have been only 4 33 × 10⁵ dynes (Fig 3)

Thus the mechanical advantage of th time course of spatial or entation of the normal papillary muscle of the normal size heart during sys ole is evident. A change in the angle that the papillary muscle forms with the mitral valve orifice from 45 to 90° causes almost a 30 per cent reduction in the force that must be developed by the papillary muscle in spite of an increase of intraventricular pressure during systole To realize the magnitude of the re duction in force consider that the theoretic accumu lated force for a papillary muscle for one day using only peak systolic tension in calculations is 19 tons [8] Thus loss of the mechanical advantage alone of the papillary muscles in the dilated heart because of the unfavorable time course of spatial orientation of the muscles during systole would result in an increase in force developed of 5 7 tons per day for both papillary muscles Because the dilated heart is a sick heart with poorly functioning myocytes its papillary muscles must perform this increased work at a time when they are not able to contract prop erly Since there may be disease of the coronary cir culation as well as an increase in myocardial tension the papillary muscles would be even more prone to ischem c damage

It should be noted that the force developed by the papillary muscles is also exerted on the ventricu lar wall This force aids in ventri ular contraction. As the ventricles dilate the mechanical advantage normally attained by the migration of the papillary muscles during systole is lost and therefore the papil lary muscles exert less effective force on the ventricu lar wall aiding less effectively in ventricular empty ing

Thus a changing angle of traction of the papillary mu cles due to the dynamic time course of spatial orientation of these muscles during the cardiac cycle

is important in determining papillary muscle efficiency. This efficiency is considerably less in the dilated heart.

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Letters to the Editor

Comment on improved maneuver for left heart catheterization

To the Editor

Described in the November 1971 issue (Am Heart J 82:716, 1971) was an interesting and extremely practical maneuver to be used during left heart catheterization. The author stated that by having the patient hyperextend his neck and look backward, it was extremely easy to enter the left ventricular chamber, especially if one were using the pigtail type of catheter through the femoral artery. He also noted that this maneuver could be applied to retrograde left heart catheterization by way of the brachial artery and that even in patients with some degree of aortic stenosis this maneuver made a great difference when entering the left ventricle. This method consequently reduced the amount of x rays taken during the fluoroscopy and shortened the total time of the procedure itself. Since one of our primary goals in the cardiovascular laboratory at Deborah Hospital is to employ a catheterization procedure that will obtain the detailed data as safely and as rapidly as possible, we were very much impressed with Dr. Weaver's observations. We therefore began to employ his technique in all our retrograde left heart catheterizations, especially for those in which the pigtail catheter was used by way of the femoral artery. Since that beginning, over 75 patients have been successfully studied by means of this technique and we felt it desirable to add our confirmation of the success of this method as well as to append a few of our own observations.

Patients examined by us fell into two groups.

Group 1. Sixty-seven patients with coronary artery disease were selectively catheterized using the retrograde right femoral arterial approach and employing the pigtail catheter as recommended by Judkins. In all cases the pigtail catheter was consistently advanced into the root of the aorta and immediately thereafter into the left ventricular chamber. In so doing, the Cook guidewire was immediately withdrawn when the pigtail catheter entered the root of the aorta. This method not only minimized the catheterization and fluoroscopy time for these patients, but it also shortened the time the guidewire was within the catheter and therefore eliminated the possibility of clot formation. The only exception to this series of successful examinations was encountered in a patient with significant calcified aortic stenosis. In this patient difficulty was experienced in entering the left ventricular chamber and such an entry is not nearly so easy as the brachial arterial approach.

Group 2. All the remaining patients (eight) who were catheterized using the right brachial arterial approach also experienced a significant reduction in the time required to manipulate the NIH or Sones catheter in entering the left ventricle. It should be noted, however, that we again found that this technique was not as successful in patients with severe aortic stenosis. Also, when comparing the retrograde approach by way of the brachial artery with the retrograde femoral arterial approach, it was quite apparent that when the pigtail catheter was inserted through the femoral artery the maneuver was more successful than when the catheter was inserted through the brachial artery.

In conclusion, we believe that Dr. Weaver's fortuitous discovery provides an excellent and useful method to everyone performing left heart catheterization, especially when the method of entry is the retrograde transfemoral approach using the pigtail catheter.

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Book reviews

Cardiovascular Review–1971 Heart Disease in India Edited by I A D Cruz Bombay 1971 Commerce Publications Division 140 pp

This interesting publication from India is primarily directed at the prevention of cardiovascular disease or its various complications and ultimate death It is concerned with such subjects as preventive cardiology epidemiology of heart disease in Northern India the normal electrocardiogram and vectorcardiogram cardiomyopathies and cor pulmonale in India Most of the papers contained in this volume will interest cardiologists

Prosthetic Replacement of the Aortic Valve By Lester R Sauvage et al Springfield Ill 1972 Charles C Thomas Publisher 217 pp Price $18 00

This is a good book devoted to an important clinical problem The authors have included hemodynamic as well as surgical and clinical principles in their presentations they not only discuss the structure and function of the normal and diseased aortic valve but also the prosthesis used Hydraulic and hemodynamic principles are nicely presented in simple diagrams Healing and histopathology as well as the clinical and surgical aspects are clearly discussed This volume should interest cardiologists cardiac surgeons and students at all levels of training

Biological Tissue in Heart Valve Replacement Edited by M I Ionescu M D D N Ross B Sc M B Ch B, F R C S and G H Wooler T D M D M A F R C S London 1972 Butterworth & Co 925 pp Price $75 00

This is a comprehensive review of the many problems related to prosthetic cardiac valves The contributors are mainly surgeons and the orientation is therefore from the surgical viewpoint The 37 chapters are concerned with the present status of prosthetic cardiac valves experimental background of biological tissue in valve replacement clinical applications heterografts autologous tissue valve transplantation and reconstruction in congenital heart disease and morphologic changes in the transplanted valves The many contributors are experts in their respective fields

The relatively brief chapters are all directed to the practical clinical aspects of prosthetic valves Illustrations and text are clearly presented This is a very good review of the problems related to valve replacement in man but it is unfortunately rather expensive Those who can afford it will find this volume very useful

Pathophysiology and Differential Diagnosis in Cardiovascular Disease Edited by Charles K Friedberg M D and Ephraim Donoso M D New York and London 1971 Grune & Stratton Inc 336 pp Price $15 00

Periodically papers which have appeared in the journal *Progress in Cardiovascular Diseases* are bound into a single book This is another such volume and those who subscribe to the journal already have copies of these papers nevertheless many of these physicians would no doubt like to have the papers collectively bound Some of the pathophysiologic problems included in this volume are related to chest pain pulmonary edema syncope cyanosis murmurs cardiomyopathies acute pericarditis hypertension and dissecting aneurysms The 16 papers are independently oriented—i e this is not a textbook or monograph but a collection of papers Such books do have a useful place in our general and private medical libraries.

Electrostimulation of the Carotid Sinus Nerve in Angina Pectoris By A J Dunning Amsterdam 1971 Excerpta Medica 104 pp Price $8 75

This brief monograph summarizes very nicely the use of electrostimulation of the carotid sinus nerves in the management of angina pectoris Dunning describes his own experience with the method and finds it to be useful in selected cases unresponsive to conventional procedures The booklet is divided into four parts namely carotid sinus reflex effects of stimulation of the carotid sinus nerve clinical results and circulatory and respiratory effects of carotid sinus nerve The book is a good single source of discussion of carotid sinus nerve electrostimulation for angina pectoris

Books received

THE BIOLOGICAL IMPERATIVES—Health Politics and Human Survival By Allan Chase New York Chicago and San Francisco 1971 Holt Rinehart & Winston Inc 399 pages Price $8 95

MANUAL OF PREOPERATIVE AND POSTOPERATIVE CARE Ed 2 Edited by John M Kinney M D Richard H Egdahl M D and George D Zuidema M D Philadelphia 1971 W B Saunders Company 644 pages Price $11 00

MEDICAL INTERVIEWING—A Programmed Manual Ed 2 By Robert E Froelich M D and F Marian Bishop Ph D St Louis 1972 The C. V Mosby Company 131 pages Price $5 00

ORGAN PHYSIOLOGY—STRUCTURE AND FUNCTION OF THE CARDIOVASCULAR SYSTEM By Robert F Rushmer M D Derived from CARDIOVASCULAR DYNAMICS Ed 3 Philadelph a 1972 W B Saunders Company 249 pages

THE PATHOPHYSIOLOGY AND TREATMENT OF DROWNING AND NEAR DROWNING By Jerome H Modell M D Springfield Ill 1971 Charles C Thomas Publisher 119 pages Price $9 50

TRANSLATION OF DE SUBITANEIS MORTIBUS (ON SUDDEN DEATHS) By Dr Paul Dudley White and Professor Alfred V Boursy Jamaica 1971 St John s University Press 212 pages

LASERS IN MEDICINE. By Leon Goldman M D and R. James Rockwell Jr New York London and Paris 1971 Gordon and Breach Science Publishers Inc. 385 pages.

VECTORCARDIOGRAPHY 2 Proceedings of the XI International Symposium on Vectorcardiography held in New York May 15 17 1970 sponsored by the Long Island Jewish Medical Center Edited by I Hoffman R I Hamby and E. Glassman Philadelphia and Toronto 1971 J B Lippincott Company 706 pages Price $39 50

PHYSIOLOGICAL BASIS OF REHABILITATION MEDICINE. Edited by John A Downey M D and Robert C Darling M D Philadelphia 1971 W B Saunders Company 445 pages

1971 YEAR BOOK OF SURGERY Edited by Seymour I Schwartz M D John S Najarian M D Erle E. Peacock Jr M D G Tom Shires M D William Silen M D and Frank C. Spenser M D Chicago 1971 Year Book Medical Publishers Inc 516 pages. Price $14 00

CARE OF THE SURGICAL CARDIOPULMONARY PATIENT Edited by William E. Neville M D Chicago 1971 Year Book Medical Publishers Inc. 313 pages. Price $17 50

ADVANCES IN SURGERY Vol 5 Edited by Claude E. Welch and James D Hardy Chicago 1971 Year Book Medical Publishers Inc. 354 pages Price $18 50

Announcements

Fondation de Physiopathologie Professeur Lucien Dautrebande prize

The Fondation de Physiopathologie Professeur Lucien Dautrebande will award during the year 1973 an international prize of approximately 500 000 Belgian francs ($10 000 U S) for the outstanding study submitted on human or animal physiopathology It is preferable that this study shall have therapeutic implications For further information regarding this prize please write to the office of the Foundation 35 Chaussée de Liège 5200 HUY, Belgium

Two Cardiovascular Nursing Courses

The Cardiovascular Education Program Nashville Tenn announces two courses in cardiovascular nursing for nurses The first for Licensed Practical Nurses will be a four week course running from July 21 through August 25 1972 The second for Registered Nurses will be an eight week course of classroom experiences and independent study running from October 2 through November 24 1972

For further information about these courses please contact the Education Director The Cardiovascular Education Program 1107 Eighteenth Ave. South Nashville Tenn 37203 or call 615 327-4031

American Heart Journal

August 1972 Volume 84 Number 2

Editorial

The problems of deep vein thrombosis

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Deep vein thrombosis has always been a serious complication of medical illness, surgical operations, and childbirth, but whereas we have mastered other difficulties such as infection, blood and fluid losses, and the complications of anesthesia, we have made little headway in preventing deep vein thrombosis so that its relative incidence and importance have steadily increased.

More than 100 years ago Virchow[1] described the formation of thrombus in the cusps of the peripheral veins, its propagation, and then its fragmentation to produce a pulmonary embolus. The early pathologists also noted that deep vein thrombosis and pulmonary embolism were very common findings in the absence of clinical signs, but the real significance of their work was not appreciated.

The modern clinician can approach the problem in two ways. First, he can attempt to prevent deep vein thrombosis altogether; this is the ideal to which we all strive. Second, he can try to diagnose the peripheral thrombosis as early as possible, before a pulmonary embolism occurs, so that he can treat it more easily and effectively.

Methods of prophylaxis depend on a knowledge of the etiology of deep vein thrombosis. We have made little progress in this sphere since Virchow's original hypotheses on the causes of intravascular thrombosis—changes in the blood, changes in the vessel wall, and changes in the rate of blood flow. The changes in the blood that are associated with thrombosis are not yet clearly defined and those that are known are difficult to alter. The administration of anticoagulants will often prevent thrombosis, but this is a shotgun approach in an attempt to miss none of a multitude of possible etiological factors. We do not know if the integrity and function of the vein wall changes during illness nor are we aware of the importance of minor damage to the intima, so that this second factor of the triad cannot yet be altered. The only factor of Virchow's triad that can be altered with ease is the rate of venous blood flow. Surgeons in particular have tried to increase the rate of blood flow in the limbs following surgery in an attempt to reduce the incidence of postoperative deep vein thrombosis. Unfortunately, simple measures such as early ambulation,[2] elevation of the foot of the bed,[3] and elastic stockings[4,5] have not been convincingly proved efficacious for two reasons. First, most of the studies published before 1960 were performed without careful control; second, not until the last five years have we had an easy and reliable method of diagnosing deep vein thrombosis in all patients. The latter problem has been solved with the advent of the I^{125} fibrinogen uptake test[6-9] and we can

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now detect 95 per cent of all postoperative deep vein thrombi immediately as they appear; however, the thrombi that we detect by this test are not all clinically significant. We are currently working on the assumption that any prophylaxis which prohibits the development of the fibrinogen detectible thrombus ought to have some effect on the overall incidence of thrombosis and pulmonary embolism, but this assumption may turn out to be false.

The methods of prophylaxis that have been studied with the I^{125} fibrinogen uptake test are elastic stockings,[5] general measures such as early ambulation, physiotherapy, and elastic stockings combined,[10] elevation of the legs,[11] and stimulation of the calf muscles with an electrical current.[12] Elastic stockings have been shown to be of no value, probably because the pressure exerted by a stocking is so critical that it is likely to be either too loose and so ineffective, or too tight and so reduce the rate of blood flow.[13] Even when a stocking is applied at the optimum pressure, the increase in venous volume flow is only in the region of 15 to 20 per cent, so it is not surprising that no one has shown elastic stockings to be of value. The effect of a combination of the routine methods of prophylaxis, such as early ambulation, physiotherapy, elevation of the foot of the bed, and so on, has been studied in an unselected series of patients without matched or concurrent controls.[10] This study failed to show any benefit from these measures, although when the patients were divided into different age groups the treated elderly patients did have a lower incidence of thrombosis.

Electrical stimulation of the calf muscles was suggested and was studied by Doran and White in 1967[14] and the method has recently been reassessed using I^{125} fibrinogen.[12] Stimulation reduces the incidence of postoperative fibrinogen detectable thrombi by approximately 60 per cent, but the method has not been widely accepted because of the practical inconvenience of applying the electrodes and because others have declared, without producing objective evidence, that it does not work. However, the critics of the method have not used the same form of stimulation, so their studies are not strictly comparable to those of Doran and colleagues or of Browse and Negus, and it may be that different methods of stimulation have different effects upon calf blood flow and metabolism.

A square wave electrical stimulus every two seconds, sufficient to cause a firm dorsiflexion of the foot, doubles the velocity of venous return and the arterial inflow to the calf. Some investigators[15] have suggested increasing venous velocity flow by passive flexion of the foot or by rhythmic compression of the leg with a pneumatic stocking.[16] Both of these methods are being currently investigated and the preliminary results of passive flexion show an effect similar to that of electrical stimulation.[15]

The combined results of all these studies will be of interest, for if the passive methods do reduce deep vein thrombosis then at last we will have confirmed that venous stasis plays an important role in the etiology of thrombosis. The good response to electrical stimulation does not by itself prove that venous stasis is important, since active contraction of the muscles is associated with many other changes in the metabolism and blood flow of the muscle.

The progress of this form of research suggests that in a few years we may be able to prevent development of deep vein thrombosis in many patients after surgical operations; however, no method is likely to be wholly effective and none of the methods so far described is easily applicable to sick people at home or to medical patients in the hospital. For these and for the high risk surgical patients we still have to rely on anticoagulants, for this is the only universally applicable form of prophylaxis which has been undeniably shown to reduce the incidence of fatal pulmonary embolism,[17,18] in spite of the fact that it does not reduce the incidence of I^{125} fibrinogen detectable thrombi.[19]

The alternative to prevention is early diagnosis and treatment. Since the development of the fibrinogen uptake test and the ultrasound flow detector, and the resurgence of interest in phlebography, we have had three excellent and complementary methods of diagnosis. It is not practical to screen all patients with these tests, but they can be used on those at risk, namely upon those with a previous history of pul

monary embolism and deep vein thrombosis also upon the very old and upon those patients having cachexia carcinomas and those with serious medical diseases

The simplest and quickest screening technique is to examine the major veins from the knee to the beginning of the vena cava with the ultrasound flow detector[20 21] This will not detect small thrombi developing in the calf or in the thigh muscles but such thrombi are unlikely to produce a massive pulmonary embolism The type of thrombus the ultrasound technique detects is the large and dangerous variety and this type must be immediately studied by phlebography and treated It is better to detect the thrombus when it is small and insignificant with the fibrinogen uptake test but for logistic reasons it is not practical to use this test on all patients However the use of this test should be encouraged because if the thrombus can be detected before the appearance of clinical signs the clinician can then follow the growth or regression of the thrombus over a period of approximately five days Without this additional facility the test would be of doubtful value because the majority of the small thrombi that it detects after an operation are symptomless unimportant and regress spontaneously By making daily examination the 20 per cent of thrombi that propagate[22] can be detected and treated as these are the thrombi that are likely to give rise to pulmonary emboli and leg symptoms Although the test works best if the fibrinogen is given before the thrombosis begins it is almost as reliable when the fibrinogen is given after the thrombus has formed making it possible to detect and follow established thrombi in medical cases in a similar manner[8 23]

The purpose of treatment of a small thrombus discovered in its early stages of development is to prevent its getting any bigger This can usually be achieved with anticoagulants most physicians use heparin followed by warfarin The treatment of a large thrombus which might become a fatal pulmonary embolus or cause ilio femoral vein occlusion must be more active and in this context treatment must be a form of therapy which actually removes the thrombus or at second best locks it in the legs There are two ways of removing a thrombus—pharmacologically with thrombolytic drugs (streptokinase or urokinase) or surgically Both forms of treatment should be available because although equally effective in ideal circumstances there are usually good reasons in any particular patient to contraindicate the use of one or the other For example streptokinase is contraindicated in the early post operative phase and thrombectomy cannot remove thrombi in the lower leg further more both methods fail when the thrombus is aging and adherent

The use of anticoagulants alone in a situation where phlebography has shown a large loose thrombus likely to produce a pulmonary embolus can only be justified if the physician is certain that the thrombus is not likely to fragment and embolize At the moment we do not know how to decide this problem and all clinicians have seen cases of pulmonary embolism occurring in the presence of adequate anticoagulation In these circumstances if streptokinase or thrombectomy are contraindicated up stream vein ligation or plication will prevent further embolism without a major increase in the incidence of late sequelae in the legs[24]

It cannot be too strongly emphasized that all methods of treatment must be based on an exact anatomical knowledge of the site and nature of the thrombus information which can only be obtained by phlebography

In summary we have made some progress over the past five years in prophylaxis and diagnosis of deep vein thrombosis but we have had less success in improving our methods of treatment The new methods of diagnosis should allow us to treat patients earlier although it has yet to be proved that this will reduce embolism or decrease late sequelae There are very many years of hard work between today s empirical approach and an effective method of prophylaxis for all patients or a treatment which will safely remove all thrombi and leave normal veins

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Clinical communications

Racial variations in the childhood electrocardiogram Preliminary observations

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Several standards for the normal electrocardiogram (ECG) in children are available[1-4] which take into consideration age differences but generally ignore other variables which may affect the ECG such as race sex and body build Racial differences in the ST segment and T wave precordial voltages and QRS duration in the ECG of adult American Negroes and Caucasians have been suggested[5-8] It has been our clinical impression that normal Negro children often have increased precordial voltage suggesting left ventricular hypertrophy This study was therefore undertaken to obtain preliminary comparative information on the ECG of normal American Negro and Caucasian children

Materials and methods

Standard 13 lead ECG s were obtained on 64 normal male children (33 Negro and 31 Caucasian) 5 to 7 years of age ECG s were recorded at 50 mm per second on an Electronics for Medicine DR 8 Research photographic recorder A photographic ECG recorder was used because of its generally superior frequency response compared with direct writer instruments[9,10] and also because it enabled us to compare our results with those of Ziegler[1] The frequency response for this recorder exceeds the minimum standards established by the American Heart Association[11] (see Fig 1)

The 33 Negro children were selected consecutively over a six week period from the Johns Hopkins Hospital Comprehensive Child Care Clinic (CCCC) All children in the CCCC reside in one of eight census tracts of inner city Baltimore within a two mile radius of Johns Hopkins Hospital These children are from families of low socioeconomic status Caucasian subjects were chosen from St Vincent s Orphanage in Baltimore County and the Johns Hopkins Hospital University Health Center and represented a higher socioeconomic group than the Negro subjects Children from the University Health Center were dependents of Hospital house staff or University graduate students

All subjects had a comprehensive cardiovascular examination including cuff blood pressure determination by at least two observers Height weight and chest circumference were routinely recorded Hematocrit was obtained on the day of exami

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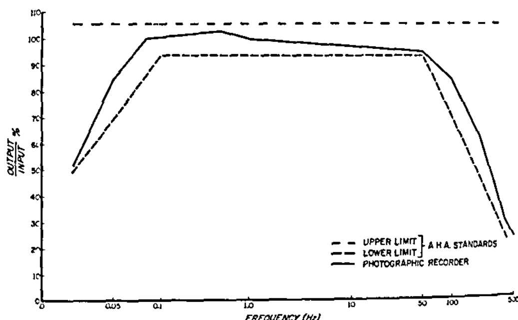


Fig. 1. Frequency response of photographic ECG recorder used in this study compared with American Heart Association minimum standard.

Table I. Physical measurements in 64 normal 5 to 7 year old male subjects

Variables	*Caucasian*	*Negro*
No. of patients	31	33
Age (yr.) (mean ± S.D.)	6.13 ± 0.91	6.47 ± 0.82
Range	5.00—7.92	5.17—7.9[illegible]
Ht. (cm.) (mean ± S.D.)	116.5 ± 7.12	117.[illegible] ± 7.36
Range	105—129	101—130
Wt. (Kg.) (mean ± S.D.)	21.9 ± 3.72	22.4 ± 4.05
Range	17.6—32.0	15.6—37.3
Chest circumference (cm.) (mean ± S.D.)	59.6 ± 2.98	58.7 ± 3.55
Range	55.7—67.3	50.9—[illegible]0.5

nation. Children with fever (exceeding 101 degrees), sickle cell anemia, hypertension, heart disease, renal disease, or other chronic illnesses were excluded from the study. All ECG's were interpreted independently by two investigators. Seven children with ECG evidence of left ventricular hypertrophy (LVH) were recalled for chest radiographs and Frank vectorcardiograms (VCG). Data from the two patient groups were compared with Student's t test.

Results

Comparison of physical measurements are summarized in Table I. There was no statistically significant difference between the Caucasian and Negro groups in height, weight, or chest circumference. Mean ages of subjects in the two groups were similar. Hematocrit values for Negroes and Caucasians were comparable and in no instance did they deviate from accepted normal values.[12]

Standard and unipolar leads. The QRS duration was significantly shorter in the Negro group ($p < 0.001$). QRS interval in Negro subjects ranged from 0.04 to 0.08 seconds with a mean value of 0.06 second and in Caucasian subjects the range was from 0.06 to 0.10 seconds with a mean value of 0.08 seconds.

There were no statistically significant

Table II. Precordial voltages in 64 normal 5 to 7 year old male subjects

Variables	*Caucasian*	*Negro*	*p value*
No. of patients	31	33	
R_{V1} (mm) (mean ± S.D.)	7.5 ± 2.67	9.2 ± 4.37	<0.10
Range	3.0—13.0	3.0—21.0	
S_{V1} (mm) (mean ± S.D.)	9.9 ± 3.71	14.2 ± 6.29	<0.005
Range	3.0—17.0	3.0—33.0	
R_{V3} (mm) (mean ± S.D.)	15.9 ± 4.66	18.6 ± 6.35	<0.10
Range	4.0—28.0	7.0—34.0	
S_{V3} (mm) (mean ± S.D.)	17.5 ± 5.98	19.0 ± 5.68	<0.10
Range	4.0—32.0	9.0—34.0	
R_{V5} (mm) (mean ± S.D.)	24.4 ± 6.23	26.6 ± 7.37	<0.30
Range	14.0—42.0	16.0—44.0	
R_{V6} (mm) (mean ± S.D.)	15.8 ± 4.27	17.4 ± 5.09	<0.20
Range	10.0—26.0	8.0—30.0	

differences between the two groups in PR or QT interval, amplitude and duration of P wave, or R wave voltage in the standard and unipolar leads. Mean frontal QRS axis was +60 degrees for Negro subjects and +80 degrees for Caucasian subjects. One Caucasian subject had left axis deviation of −56 degrees.

Precordial leads. Data on precordial lead voltages for the two groups are summarized in Table II. The depth of the S wave in V_1 was significantly greater in Negro subjects ($p < 0.005$). The S_{V1} measured from 3 mm to 33 mm with a mean value of 14.2 mm in the Negro group and 3 mm to 17 mm with a mean value of 9.9 in the Caucasian group. Rank order of amplitudes for S_{V1} for both groups showed that the highest ranking 12 subjects were Negro. S_{V1} amplitudes approximated a normal curve in both groups, with the Negroes having a wider range and a greater dispersion.

There were no statistically significant differences between the two groups for R or S wave voltages in Leads V_3 through V_6 and for R wave voltage in Lead V_1. However, a consistent tendency toward greater precordial voltages is noted in Negro subjects. Mean voltages are greater in Negroes than in Caucasians for R_{V1}, R_{V3}, S_{V3}, R_{V5}, and R_{V6}, although the differences are not statistically significant. S-T elevation or depression was not observed. One Caucasian subject showed J point elevation of 2.5 mm in the left chest leads.

Abnormal precordial voltages suggesting LVH were present in 7 subjects. ECG, VCG, and x-ray data for this group are summarized in Table III.

Discussion

Reports of racial variation in the ECG of adult American Negroes include ST-T changes, increased voltages, and shortened QRS duration.[5, 8] Thomas, Harrison, and Lassiter[4] in a study of 370 healthy young Negro adults found ST segment elevation in the left precordial leads in 27 per cent of male subjects. Gottschalk and Craige[6] in a comparative study of Negroes and Caucasians found a higher incidence of ST segment elevation among Negroes. Wasserburger[3] called attention to persistence of the juvenile pattern of T wave inversion in right chest leads in healthy adult male Negroes. However, other investigators have disputed this finding.[13] Lipberger and co-workers[7] in an analysis of the orthogonal ECG and VCG in 518 normal men found Negroes to have significantly shorter QRS intervals and greater maximal spatial vectors. ST-T changes or increased QRS voltage have also been reported in the South African Negro,[14, 16] Ceylonese,[17] West Indians,[18] Peruvians,[19] Japanese,[20] and populations in India.[21]

Table III. Seven subjects with electrocardiographic diagnosis of left ventricular hypertrophy

Subject	Race	Age (yrs)	ECG						
			Precordial voltage (mm)				Overall rotation		
			S_{V1}	R_{V5}	R_{V6}	Q_{V6}	Frontal	Horizontal	[illegible]
C M	Negro	7 04	24	44	30	4	Figure of eight	CCW	CCW
G J	Negro	7 02	16	42	29	2	Figure of eight	CCW	CCW
J G	Caucasian	6 00	14	42	26	5	CW	CCW	CCW
J W	Caucasian	5 45	15	38	24	3	CW	CCW	CCW
T G	Negro	6 77	8	40	24	2	CW	CCW	CCW
M M	Negro	5 25	33	17	14	2	CW	CCW	CCW
K B	Negro	7 37	24	19	16	2	CW	CCW	CW

Maximal spatial vector to the left (Normal = 1 1 to 2 0 mv)
†Sum of maximal spatial vectors to the left (LMSV + 10 msec vector preceding LMSV + 10 msec vector following LMSV)
‡Sum of maximal left and posterior vectors (Normal = < 3 5 mv)

Our findings indicate that American Negro male children have significantly deeper S_{V1} than do Caucasian controls. African investigators have made similar observations regarding racial differences in the ECG. Walker and Walker[16] found greater precordial voltages (maximum R + S) in South African Bantu male children as compared to Caucasians, and Sutin and Schrire[15] reported S_{V1} to be greater in Bantu newborns than whites. Aschcroft and associates[22] reported S_{V1} to be significantly greater in African than in Indian counterparts in Guyana.

Possible factors in the genesis of these racial variations in the ECG include body habitus, composition, and nutrition. Correlation between ECG parameters and body build has been reported in adults[7, 23, 4] but is disputed in children.[2] Negro subjects in this study differed slightly in body build compared with Caucasian subjects, as indicated by the greater mean weight and height and smaller mean chest circumference for the Negro group. However, there were no apparent relationships between precordial voltages and height, weight, or chest circumference in either group. Those patients with abnormal QRS voltage (Table III) did not show any significant difference in body build.

Differences in body composition as a source of variation in the ECG have been suggested by other investigators.[7] Experimental work indicates Caucasian male children have proportionately more body fat than Negro controls.[6] While it is often suggested that obesity is responsible for decreased precordial voltages,[7] experimental evidence for this is lacking. Individual variation in torso dimension or skin resistivity[27] have also been suggested as possible explanations for tall precordial potentials.

Chronic severe anemia has been incriminated as a cause of tall precordial voltage in the left chest leads, presumably due to the high output state.[8] In the present study there were no anemic subjects and no apparent relationship between hematocrit and ECG voltages.

Our findings of shorter QRS duration in Negro male children agree with the observations of Pipberger and associates,[7] who found the mean QRS duration in normal adult male Negroes to be 7 msecs less than

s		VCG spatial scalar measurements			Chest x ray
Direction initial forces	Azimuth (degrees)	LMSV (mv)	Sum of LMSV† (mv)	Sum of max LI SV‡	(CTR)
t Right Inf	+20	2 ?3	4 36	5 13	0 53
t Inf	−34	1 75	3 15	2 54	0 56
t Right Inf	−70	1 57	3 15	2 83	0 40
t Inf	−42	1 70	3 ??	1 4?	0 53
t Right Inf	+17	1 35	? 73	2 14	0 4?
t Right	−18	1 57	3 69	? 76	0 5
t Right Inf	−45	1 47	3 45	2 81	0 45

SI (mv)

in adult male Caucasians These findings suggest that the diagnosis of conduction defects in Negroes may be obscured by racial variation Racial differences in the anatomy of the conducting system is an intriguing but undocumented explanation for these discrepancies

The ECG diagnosis of LVH in children is commonly based on the magnitude of precordial voltage Accepted normal standards employed are generally those of Ziegler[1] For the purposes of this study the diagnosis of LVH by magnitude of precordial voltage was defined as R_{V6} or S_{V1} which exceeded two standard deviations from the mean[4] These values taken from Cassels and Ziegler s tables[29] were $S_{V1} = 24$ mm and $R_{V6} = 21$ mm Because of the poor reliability of combined criteria for ventricular hypertrophy[2] (e g $S_{V1} + R_{V6}$) in children no attempt was made to use such criteria as parameters of LVH in this study

Seven subjects had precordial voltage which exceeded normal accepted ECG standards (Table III) Five of these children were Negro and two were Caucasian All subjects in the group were asymptomatic and had no evidence of cardiovascular disease

A VCG was performed on these children to determine whether increased precordial potentials represented abnormal posterior forces indicative of LVH Spatial and loop analysis of VCGs were compared with available normal values for children[30]

Two of the 7 (J W and G J) had radiographic evidence of mild cardiac enlargement with prominent left ventricular contours (Fig 2 *A* and *B*) Spatial measurements of the VCGs in these subjects were normal although the horizontal loop of subject J W is oriented posteriorly (Fig 3*A*) with a maximal spatial vector at the upper limits of normal Two other subjects (C M and M M) had borderline cardiac enlargement The VCG of C M suggests LVH with increased maximal spatial vector and summed maximal left and posterior vectors (Fig 3*B*) Three children (J G T G and K G) are examples of LVH determined by magnitude of precordial voltage only Two of these children had only deep S waves in the right precordial leads and one demonstrated tall left chest potentials VCGs and chest x rays were



Fig. 2. *A* and *B*. Posteroanterior chest radiograph in two subjects with left ventricular hypertrophy determined by magnitude of precordial voltage. *A*, Subject J. W. Cardiothoracic ratio is 0.53 and prominence of left ventricular contour is present. *B*, Subject C. M. Borderline cardiac enlargement is shown with cardiothoracic ratio 0.53.

within normal limits in these three patients.

There are several possible explanations for the diagnosis of LVH determined by the magnitude of precordial voltage encountered in the seven subjects in this study. First, accepted normal standards for the childhood ECG may be too restricted. Certainly the tables of Ziegler[1] which are generally regarded as the basis of the normal childhood ECG utilized a relatively small number of subjects and may not provide a representative sample. For example, the normal limits for S_{V1} in 5- to 8-year-old children is based on only 44 subjects.

It is difficult to fully explain the findings in the two patients (J. W. and G. J.) with ECG, VCG, and radiographic evidence suggesting LVH. Perhaps these subjects represent an early form of endomyocardial disease or idiopathic hypertrophic subaortic stenosis since the absence of any cardiovascular signs or symptoms generally excludes other forms of congenital or acquired heart disease. Since all 7 subjects with LVH determined by the magnitude of precordial voltage are asymptomatic and without signs of cardiovascular disease, it is perhaps most reasonable to regard them as normal variants. Further clinical studies are being conducted on a larger group of children with LVH determined by voltage to clarify the factors responsible for this ECG abnormality.

The purpose of this pilot study was to determine whether ECG differences between Negro and Caucasian children could be documented. Five- to seven-year-old male children were selected for study in order to provide as homogeneous a population as possible and also because of our clinical impression that this group of children was most likely to yield positive results. However, it is quite possible that other studies utilizing different age groups, female children, or large populations may offer further substantiation of ECG differences between Negro and Caucasian American children.

Summary

A comparative ECG study of 64 normal male Negro and Caucasian children revealed deeper S_{V1} and shorter QRS duration in Negro subjects. These findings suggest that normal ECG standards for children may require adjustment for race. The clinical features of seven subjects with left ventricular hypertrophy (LVH) determined by voltage are discussed.

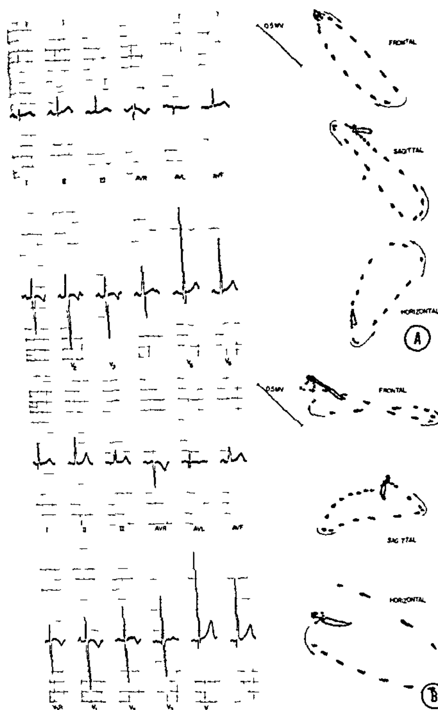


Fig 3 *A* and *B* ECG and VCG in two subjects with left ventricular hypertrophy determined by magnitude of precordial voltage *A* Subject J W ECG demonstrates tall voltages in left chest leads (R_{V_6} = 24 mm) VCG shows a relatively narrow loop directed posteriorly with a maximal spatial vector to the left of 1 70 mv *B* Subject C M ECG shows tall voltages in left chest leads (R_{V_5} = 30 mm) VCG is normal ECGs are recorded at standard ×2

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Factors influencing hemolysis in valve prosthesis

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In 1954 Rose and associates[1] reported for the first time hemolytic anemia associated with intracardiac valve prosthesis This complication was then experimentally confirmed in dogs by Stohlman and co workers[2] in 1956 It is now a well recognized syndrome but the etiological factors are still not well defined The purpose of this study was to evaluate the hemolytic effects of prosthetic materials and designs

Materials and methods

The 208 patients included in this study represent all the patients with valve replacement who attended the anticoagulant clinic from July 9 1970 to Sept 13 1970 a period arbitrarily chosen These were from a group of 757 patients who had valve replacement in this hospital from Jan 4 1962 to July 15 1970

The types and positions of valve prostheses are shown in Table I The degree of hemolysis was evaluated in all these patients with various types of prostheses But only the Starr Edwards and Beall prostheses were studied with respect to etiological factors of hemolysis The Beall prosthesis is a Teflon disc valve with Teflon covered cage Starr Edwards valves are of different types (1) silicone elastomer ball uncovered cage models 1000 1200 and 1260 for the aortic valve and models 6000 6100 and 6120 for the mitral orifice (2) Stellite ball Teflon covered cage models 6300 and 2300 for mitral and for aortic orifices respectively These were reported as functionally stenotic[3,4] and have been replaced recently by models 6310 and 2310 These newer models have a large orifice and a slight modification of the Teflon ring (composite seat)

Screening laboratory tests for evidence of hemolysis performed in all these patients comprised the following (1) hemoglobin (Hb) and hematocrit (Hct) (2) free plasma hemoglobin by colorimetry (normal values less than 5 mg per 100 ml) (3) direct and indirect Coombs test (4) serum lactic dehydrogenase activity (SLDH) using the Cabaud Wroblewski method (normal values less than 500 u C W) and (5) serum hydroxybutyryl dehydrogenase (HBD) using Rosalki s technique[5] (normal values less than 300 u)

Sixty eight patients had normal results

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Table I. Types and positions of single and multiple prostheses

Positions	Starr Edwards			Beall	Surgitool	Hufnagel	Magovern	Others
	Silicone elastomer ball	Stellite ball	Disk					
Isolated								
Mitral (M)	51	36	2	12	—	1	—	—
Aortic (A)	33	27	—	—	1	2	1	—
Tricuspid (T)	2	—	—	—	—	—	—	—
								Total = 171
Multiple								
M + A	13	6	—	—	—	—	—	1
M + T	—	—	—	3	—	—	—	3
M + A + T	—	—	—	—	—	—	—	5
								Total = 37

Table II. Criteria of hemolysis

Variables	Mild hemolysis	Severe hemolysis
SLDH activity (I/II < 0.8)	500–1500 u	> 1500 u
Free plasma Hb	< 50 mg./100 ml.	> 50 mg./100 ml.
Urinary Hb	absent	present
Reticulocytes	1.5–10%	> 10%
Plasma total bilirubin	1–3 mg./100 c.c.	> mg./100 c.c.
Schistocytes	absent	present

and no other tests were performed. In 140 patients in whom one or more of the above parameters were abnormal, the same tests were repeated and the following investigation was also carried out.

(1) Colorimetric ratio of SLDH subunits (Profile SLDH, General Diagnostics).[7,8] Normal ratios of I over II subunits are 0.8 to 1.2. Ratios of less than 0.8 suggest II subunits predominance and are compatible with hemolysis, muscle injury, renal infarction, and megaloblastic anemia.

(2) Peripheral blood smear for search of schistocytes and megaloblastosis.

(3) Reticulocyte count (normal values less than 1.5 per cent).

(4) Total and direct bilirubin levels were determined by Hogge and Meites method[9] (normal values less than 0.8 and 0.2 mg. per 100 ml., respectively).

(5) Qualitative determination of urinary hemoglobin.

(6) Serum haptoglobin was also determined in 19 cases by immunodiffusion (Partigen Behringwerke A.G.)[10] (normal values between 20 and 204 mcg. per 100 ml.).

The criteria of hemolysis and of its severity were determined as indicated in Table II. It was evaluated primarily by the SLDH levels whenever I/II was smaller than 0.8. SLDH activity[11] correlates well with erythrocyte survival time. SLDH levels of 500 u. and less represent normal half life, levels of 500 u. to 1500 u. correspond to 15 to 25 days, considered as mild hemolysis, and levels greater than 1500 u. correspond to a survival of less than 15 days reflecting severe hemolysis.[12] In a few cases of normal SLDH activity or discordant liver/heart (I/II) ratio, the diagnosis of hemolysis was based on the other parameters.

Anemia was defined by a Hb of less than 10.5 Gm. per cent. Therapy of anemia was not considered because of the various iron preparations and dosages.

All patients were ambulatory. All had a

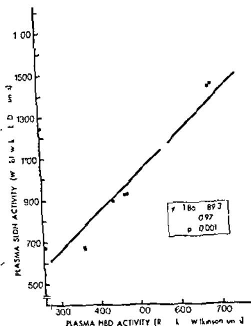


Fig 1 The relation between SLDH activity (L/H subunit ratio < 0 8) and HBD in 63 consecutive cases

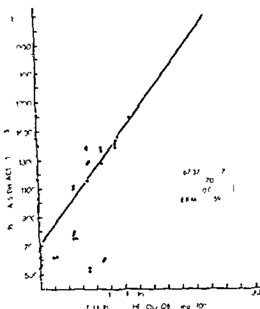


Fig 2 The relation between SLDH activity and free plasma hemoglobin in 119 consecutive cases

phonocardiogram using an Electronics for Medicine five channel photographic recorder to detect signs of ball variance[12] Acute myocardial infarction was excluded by history and ECG

Results

1 *Incidence and degree of hemolysis* Of the 208 patients studied 140 (67 3 per cent) showed unequivocal signs of intravascular hemolysis Severe hemolysis was present in 22 4 per cent All these 140 cases except 4 had abnormally high SLDH levels The SLDH subunits ratio determined in these 136 patients was abnormal with H predominance (L/H < 0 8) in 114 abnormal with L predominance (L/H > 1 2) in 4 whereas it was normal in 18 An excellent correlation existed between SLDH and HBD plasma levels (Fig 1) SLDH levels with L/H ratio < 0 8 plotted against free plasma hemoglobin were found also highly significant (Fig 2) However only 3 patients had circulating hemoglobin exceeding 50 mg per 100 ml Urinary Hb determined qualitatively in 140 patients was positive in only 26 Almost all these 26 patients presented high levels of SLDH and free Hb was present often in high amounts but no correlation was found between urinary Hb and the other parameters Since only 19 patients had plasma haptoglobin determinations (mean 9 73 mcg per 100 c c) the correlation between haptoglobin and urinary hemoglobin was not attempted Bilirubin determination was made in 140 patients In only 26 did the total bilirubin exceed 0 8 mg and although SLDH HBD and plasma hemoglobin levels were high in all cases no correlation was found between these parameters The highest total and direct bilirubin values were 2 25 mg and 1 20 mg per cent respectively

Forty-one and four tenths per cent of these 140 patients with hemolysis had an abnormal Hb (<13 Gm per cent) 17 patients had a Hb between 10 5 and 12 Gm per 100 ml and 31 had Hb levels between 12 and 13 Gm per 100 ml In only 7 1 per cent was it significantly low (< 10 5 Gm per 100 ml)

Reticulocyte count in the peripheral blood smear was superior to 1 5 per cent in 133 of 136 cases The highest value was 17 8 per cent and the mean value for the group was 3 84 per cent ± 0 23 S E M No correlation was found between reticulocyte count and SLDH levels Schistocytes were

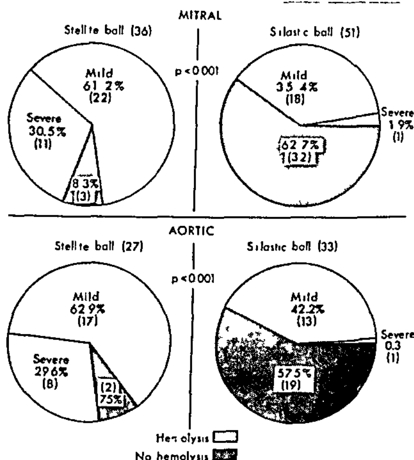


Fig. 3. Comparison between the degree of hemolysis produced by silicone elastomer ball uncovered and Stellite ball covered Starr-Edwards valve. Statistical analysis was performed by chi square test.

present in only 17 of 140 patients who had their peripheral blood smear examined. Of these 140 patients, 10 had a Hb level of less than 10.5 Gm. per 100 ml., and of these 9 had schistocytes. All had more than 2,000 u. SLDH and a high percentage of reticulocytes. Megaloblastosis was excluded in all these cases. Direct Coombs test was negative in all of 208 patients, although 10 had a positive indirect test.

In summary, the diagnosis of hemolysis was based on an increased SLDH activity with L/H < 0.8 in 114 patients. In the other 26 patients, hemolysis was determined by increased HBD levels, free plasma hemoglobin and high reticulocyte count.

2. *Influence of the types of prostheses and its materials.* All 12 patients with a mitral Beall prosthesis had hemolysis: mild in 6 and severe in the other 6. Mean SLDH level was 1594 ± 123 (S.E.M.), which is higher than the mean SLDH level found in cases of multiple prostheses irrespective of their types. One of the patients with a Beall valve had severe hemolytic anemia resistant to iron therapy.

The incidence and degree of hemolysis were greater in cases of Stellite ball covered valves as compared to those of silicone elastomer ball uncovered prostheses, irrespective of position, aortic or mitral (Fig. 3). SLDH activity was significantly higher in cases of Stellite Teflon covered prostheses for aortic valves as well as for mitral valves (Fig. 4).

3. *Influence of the position of the prostheses.* No significant difference was found between 67 aortic and 101 mitral prostheses of all types (Fig. 5). The same results were observed when comparing mitral to aortic Starr-Edwards valves as a group and when these valves were studied separately as Stellite ball covered valves and as silicone elastomer ball uncovered valves.

4. *Influence of number of prostheses.* Of 32 patients with a double prosthesis (including all models of valves), 26 (81.2 per cent) presented hemolysis of which half was severe. Hemolysis was found in 109 of 141

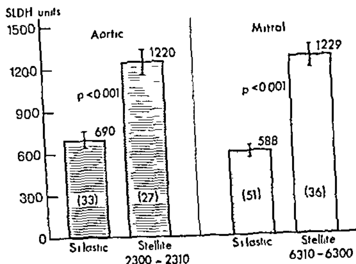


Fig 4 Comparison between SLDH level found in patients with Starr Edwards mitral and aortic valves Significantly higher levels of SLDH were found for Stellite valve Teflon covered prostheses (t test)

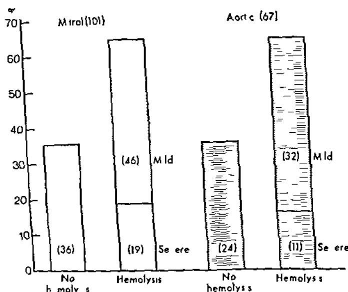


Fig 5 Degree of hemolysis found in patients with mitral and aortic prostheses irrespective of design

es of single prosthesis (63 7 per cent) DH activity was significantly higher in it group as compared to the single valve oup (Fig 6) Four patients had severe molytic anemia in this group of double osthesis (12 5 per cent) contrasting with incidence of 5 6 per cent in the single lve group

Double mitral and aortic Starr Edwards licone elastomer ball valves hemolyzed more than single mitral and aortic valves of the same model (Fig 7) but no difference was noted between Stellite ball covered valves (1 615 ± 154 versus 1 224 ± 60 S E M SLDH u)

The incidence of hemolysis was similar for triple and double valve prostheses including all models

5 *Influence of valve orifice size* The only significant difference with respect to orifice

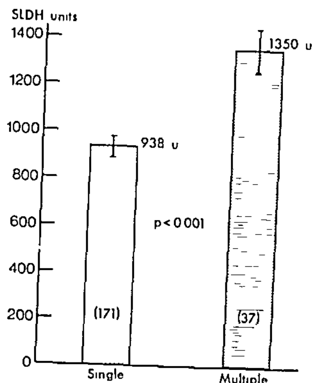


Fig 6 SLDH activity found in patients having a single and a multiple valve replacement irrespective of design (t test)

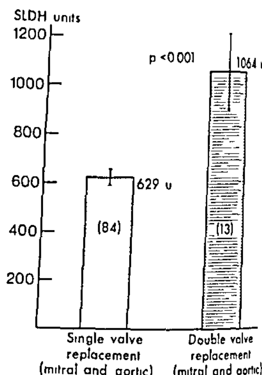


Fig 7 SLDH activity found in patients having single and double (mitro-aortic) Starr Edwards Stellite ball uncovered prostheses (t test)

size was observed between the 2300 and the 2310 models of the aortic Starr Edwards Stellite ball valves The 2300 model having a smaller orifice had a significantly higher incidence of hemolysis (Fig 8) This was not observed for mitral valve models 6300 and 6310 having similar orifice size differences

6 *Other factors studied* The mean time elapsed since the operation was not different between the hemolyzing and non hemolyzing prostheses Ball variance was not observed by phonocardiographic screening Prosthesis dysfunction was not suspected clinically and it was not found in the 12 patients who had a postoperative hemodynamic study The influence of rhythm was not studied

Discussion

Subclinical hemolysis was detected in 67 per cent of these 208 patients This finding is in agreement with previously reported series [14, 19] Chronic hemolytic anemia resistant to iron therapy was present in only 5 per cent of our patients an incidence similar to that reported by Rodgers and Sabiston [6] The best method for estimating the degree of hemolysis is the erythrocyte survival time obtained by ^{51}Cr [21] Shortened erythrocyte half life has been reported also in severe unoperated rheumatic heart diseases [18, 2] However, this method although very sensitive, is expensive and time consuming It appears that total SLDH activity gives a reliable approximation of erythrocyte survival time [11, 12] It is unfortunately much less specific since it is also increased by diseases involving liver kidney skeletal and cardiac muscle [1] The specificity of the test may be fostered by determining its origin by electrophoretic separation of its isoenzymes [24] or by fractionation of H and L subunits (by heat or substrate inhibitors) [7, 8] The latter method was used in this study In addition faster moving LDH isoenzymes reduce alphaketobutyrate more readily then slow moving ones and thus the quantitation of this reaction may be expressed as alpha hydroxybutyrate dehydrogenase activity (HBD) [4] Consequently, plasma LDH originating from heart kidney and erythrocyte should correlate well with HBD levels a fact confirmed in this study as shown in Fig 1

Free plasma hemoglobin liberated from erythrocytes binds to haptoglobin or is excreted by the kidney whenever the plasma levels exceed the binding capacity

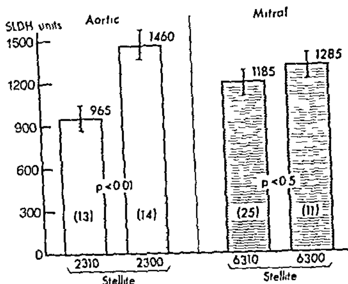


Fig 8 Difference between two models of Stellite ball covered prostheses were apparent only for the aortic group (t test)

of this protein Normally sufficient haptoglobin is present to bind 100 to 150 mg of hemoglobin per 100 c c[25] As shown in Fig 2 we found a relatively good correlation between SLDH and free Hb although the degree of dispersion suggests that haptoglobin production or its ability to bind free Hb may be different from patient to patient with chronic hemolysis Haptoglobin levels were determined in only 19 cases and were found decreased in cases with high SLDH activity Slight hyperbilirubinemia was observed in a few cases as expected since only slight to moderate hemolysis of extravascular origin is observed in these cases of valve prostheses[26 27]

Abnormal erythrocyte morphology may be observed in peripheral blood smear in cases of hemolysis[28] As in microangiopathic anemia fragmented red cells or schistocytes always reflect intravascular hemolysis but usually when it is severe[9] In our experience SLDH activity has been more reliable In this series only 12 per cent of the patients presenting with hemolysis had schistocyte All of these showed severe erythrocyte destruction and 50 per cent had significant hemolytic anemia (Hb < 10 5 Gm per 100 ml) This latter finding contrasts with the 7 1 per cent incidence of severe anemia in patients with hemolysis Although microangiopathic anemia and intravascular hemolysis following prosthetic valve replacement have some features in common they differ in that the erythrocyte fragmentation in the former condition is associated with fibrin deposits and hypofibrinogenemia as described by Brain[30] In contrast patients with prosthesis hemolysis show a tendency to hyperfibrinogenemia secondary to a low rate catabolism or to an increased synthesis[31]

Increased turbulence generated by the impact of red cells on rough and hard surfaces has been incriminated as the most important etiologic factor of this hemolytic phenomenon associated with valve prosthesis[13 20 32 35] Greater hemolysis during exercise has been reported particularly in cases of aortic prostheses[18 19 36] in the presence of ball variance and in paravalvular leaks[19 38 39] These facts favor the turbulence hypothesis which indirectly is also supported by the observation that properly functioning heterografts are only slightly hemolytic[40] Hemolysis has also been experimentally produced by Bull[41] using a pump system where turbulence is created by a rapidly moving blood stream in the presence of an obstruction The autoimmune mechanism involving erythrocyte antibodies generated by antigenically active red cell fragments suggested by Pyrofsky and associates[42 43] in 1965 may be a secondary phenomenon

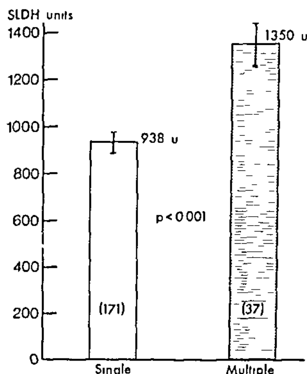


Fig. 6 SLDH activity found in patients having a single and a multiple valve replacement irrespective of design (t test)

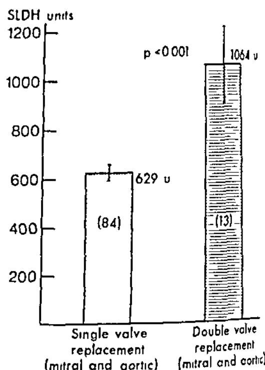


Fig. 7 SLDH activity found in patients having single and double (mitro-aortic) Starr Edwards Stellite ball uncovered prostheses (t test)

size was observed between the 2300 and the 2310 models of the aortic Starr Edwards Stellite ball valves. The 2300 model having a smaller orifice, had a significantly higher incidence of hemolysis (Fig. 8). This was not observed for mitral valve models 6300 and 6310 having similar orifice size differences.

6. *Other factors studied.* The mean time elapsed since the operation was not different between the hemolyzing and non-hemolyzing prostheses. Ball variance was not observed by phonocardiographic screening. Prosthesis dysfunction was not suspected clinically and it was not found in the 12 patients who had a postoperative hemodynamic study. The influence of rhythm was not studied.

Discussion

Subclinical hemolysis was detected in 67 per cent of these 208 patients. This finding is in agreement with previously reported series.[14, 19] Chronic hemolytic anemia resistant to iron therapy was present in only 5 per cent of our patients, an incidence similar to that reported by Rodgers and Sabiston.[20] The best method for estimating the degree of hemolysis is the erythrocyte survival time obtained by ^{51}Cr.[21] Shortened erythrocyte half life has been reported al[so] in severe unoperated rheumatic heart di[s]eases.[18, 2] However, this method althoug[h] very sensitive is expensive and time con[]suming. It appears that total SLDH ac[]tivity gives a reliable approximation o[f] erythrocyte survival time.[11, 12] It is un[]fortunately much less specific since it i[s] also increased by diseases involving liv[er] kidney skeletal and cardiac muscle.[3] Th[e] specificity of the test may be fostered b[y] determining its origin by electrophoreti[c] separation of its isoenzymes[4] or by frac[]tionation of H and L subunits (by heat o[r] substrate inhibitors).[7, 8] The latter metho[d] was used in this study. In addition faste[r] moving LDH isoenzymes reduce alpha-keto[] butyrate more readily then slow movin[g] ones and thus the quantitation of this reac[]tion may be expressed as alpha hydrox[y] butyrate dehydrogenase activity (HBD). Consequently plasma LDH originatin[g] from heart kidney and erythrocyte shoul[d] correlate well with HBD levels a fact con[]firmed in this study as shown in Fig. 1.

Free plasma hemoglobin liberated fro[m] erythrocytes binds to haptoglobin or i[s] excreted by the kidney whenever th[e] plasma levels exceed the binding capacit[y]

Summary

Hemolysis was found in 67 3 per cent of 208 patients with valve prosthesis The diagnosis of hemolysis was based on an increased serum lactic dehydrogenase activity (SLDH) with sub unit liver/heart < 0 8 in 114 patients In the others it was determined by increased serum hydroxybutyryl dehydrogenase (HBD) free plasma hemoglobin and abnormally high reticulocyte count Excellent correlations existed between SLDH and HBD plasma levels on the one hand and between SLDH levels and free plasma hemoglobin on the other Significant hemolytic anemia (hemoglobin < 10 5 Gm per 100 ml) was observed in only 5 per cent of these patients irrespective of iron replacement therapy The Beall mitral prosthesis was found the most prone to hemolysis, a complication observed in all 12 cases studied The Starr Edwards Stellite ball Teflon-covered valve hemolyzes significantly more than the silicone elastomer ball uncovered prosthesis in the aortic and mitral positions It is felt that the Teflon covering may be an important hemolytic factor in both Starr Edwards model and Beall prostheses

The authors wish to thank Dr Paul David General Director Montreal Heart Institute and Dr Pierre Simard Chief of Clinical Laboratorie Montreal Heart Institute as well as Dr Joseph Pellerin for their support and collaboration in this study We are also grateful to Mr Samir Naoum Mr Raymond Guay and Mr Lise Dumas for their technical help and assistance

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Our findings suggest that prosthetic materials may be major determinants of this hemolytic syndrome. Hemolysis is significantly more prevalent in cases of Stellite ball Teflon covered Starr-Edwards valve as compared to the silicone elastomer ball cage prosthesis irrespective of their mitral or aortic position. These prostheses being different in two aspects, the ball material and the Teflon covering, the relative importance of these characteristics with respect to hemolysis is difficult to assess. It is possible, as suggested by Myhre and co-workers[44] that the impact on red blood cells by the metallic ball is greater and is thus more hemolyzing. The aortic and mitral position of the prosthesis may not differ in this respect. On the other hand, Teflon covering may also produce hemolysis by lack of epithelium covering as previously reported for Teflon patches closing interatrial and interventricular septal defects.[4, 47] Be this as it may, the Stellite ball and Teflon covered prostheses are definitely more prone to hemolysis and it appears that the Teflon covering may be the most important factor. It also seems that these characteristics are more significant than the hemolytic effect of increased turbulence, at least in these prostheses. In fact the aortic valve produces more turbulence as compared to the mitral[48] and yet identical mean SLDH levels were found for Starr-Edwards metallic ball cloth covered aortic and mitral prostheses. Likewise, no statistically significant difference was found between the mitral and the aortic silicone elastomer ball uncovered valves, although SLDH levels in the aortic prosthesis were slightly superior. This slight difference for uncovered prostheses which are less prone to hemolyze may be explained by the increased turbulence at the aortic position. Hemolysis most likely associated with turbulence was noted in cases of aortic Starr-Edwards model 2300 which has a covered cage but is in addition functionally stenotic.[3, 4] Double prostheses, aortic and mitral, as compared to single aortic and mitral prostheses show a higher degree of hemolysis only for the cases of silastic ball uncovered prosthesis, which, as previously mentioned, are less prone to hemolysis. The turbulence factor is most likely more prevalent in these double prostheses and explains the higher degree of hemolysis. However, no significant difference was noted in cases of metallic ball Teflon covered valves, suggesting that the Teflon covering and the Stellite ball characteristics prevail over the turbulence factor. The hemolytic effect of turbulence may not be decreased in the presence of Teflon covering since hemolysis is more frequently observed in such cases, but it appears to be overshadowed by the effects of the Teflon and/or of the Stellite ball and thus it may not be recognized. The Beall prosthesis, a disc valve but which also has a Teflon covered cage, is likewise very hemolyzing.[49] SLDH levels found in this group were higher than those observed in plurivalvulars where turbulence may play an important role. Mitral gradients have been documented after Beall valve replacement[50] and hemolysis may certainly be due at least in part to increased turbulence. But their hemolytic tendency is so great that turbulence does not appear to be the only factor, and possibly not the most significant. It therefore seems that Beall valves combine two hemolyzing factors, one related to the turbulence and the other to the cage covering and this association may explain their greater tendency to hemolyze. It may be that the Teflon covering is the most important hemolytic factor in both Starr-Edwards and Beall prostheses since this characteristic is common to both.

Hemolysis associated with valve prosthesis is well tolerated and responds well to iron replacement therapy. If severe, the bone marrow cannot compensate by increased erythropoiesis and resistant anemia develops. Tachycardia secondary to anemia may increase turbulence and hence the hemolytic process. Other forms of treatment, specifically steroids[33-31] and splenectomy,[31, 51] have not been successful.

Long-term effects of chronic intravascular hemolysis have not yet been completely established. Anemia and renal hemosiderosis seem to be its major harmful effects. Anemia resistant to iron treatment is present only in a small percentage of cases and renal hemosiderosis does not seem to impair renal function.[7] However, long-term effects of hemosiderinuria have not yet been adequately documented.

The incidence of hypertension and associated factors
The Israel ischemic heart disease study

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Scientific reports on the incidence of hypertension are extremely uncommon In the present paper we have used available data from a large scale prospective study focussed principally on coronary heart disease to add to existing knowledge about hypertension incidence We are fully conscious of the limitations implied in our dependence on single casual blood pressure readings to define persons at risk and persons developing elevated blood pressure levels but single casual readings have been shown to be valuable tools in the analysis of coronary heart disease incidence [1] Perhaps they can be usefully employed in the definition and study of hypertension incidence as well

Methods

The data are from a five year prospective study of 10 000 Israeli male civil service workers which has been described elsewhere [2] Briefly the study design took advantage of the heterogeneity of backgrounds in the Israeli population and selected men born in six areas Israel Asia except Israel Africa Eastern Europe Central Europe and Southern Europe from a population of male civil service employees aged 40 and over in 1963 The population included such diverse groups as dockworkers clerks street cleaners and judges so the common picture of a civil service employee as a sedentary clerical worker is not completely applicable in this study

Blood pressures were measured on the right arm (with the subject lying down) at examinations in 1963 1965 and 1968 by the method recommended by WHO [3] reading the pressure at eye level Systolic pressure was measured at the onset of the sounds and diastolic pressure at the point of disappearance of the Korotkoff sounds

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nurses subjects were asked about the number of portions of specific food items that they usually ate on a weekly basis Portion sizes were referenced to food models on display and the numbers of small medium or large portions of each food were first converted to grams of each food and then to nutrients for each food by means of multipliers stored in the computer memory and corresponding to gram units of each food The nutrients for each food were then summed into a weekly total for each subject All variables and measurements in the list refer to the 1963 examination

1 *Year of immigration to Israel* 1938 or before 1939 1948 1949 and later
2 *Number of children* (includes stillbirths and those who have died) ≦ 1 2 3 4+
3 *Number of persons living together* (includes only those eating with you in your home) ≦ 3 4 5+
4 *Number of rooms in your home* (excludes kitchen bathroom balconies and small entrance hall) ≦ 2 3 4+
5 *Weight/height ratio* (kilograms/centimeters) ≦ 0 39 0 40-0 45 0 46+
6 *Triceps skinfold* (in millimeters) ≦9 10 14 15+
7 *Subscapular skinfold* (in millimeters) ≦14 15 21 22+
8 *Total serum cholesterol* (in milligrams per cent) ≦189 190-219 220+
9 *Cholesterol in α lipoprotein* (in milligrams per cent) ≦31 32 39 40+
10 *Cholesterol in β lipoprotein* (in milligrams per cent) ≦149 150-189 190+
11 *Per cent of total cholesterol in α lipoprotein* (in milligrams per cent) ≦15 16-19 20+
12 *Uric acid* (in milligrams per cent) ≦4 4 4 5-4 9 5 0+
13 *Hemoglobin* (in grams per cent) ≦14 4 14 5 15 4 15 5+
14 *Hematocrit* (in per cent) ≦44 45-46 47+
15 *Persons per room* (crowding index derived from No 3 and No 4) ≦1 00 1 01 1 99 2 00+
16 *Total protein* (in grams per week) ≦649 650 799 800+
17 *Animal protein* (in grams per week) ≦299 300-399 400+
18 *Total fat* (in grams per week) ≦499 500-699 700+
19 *Saturated fat* (in grams per week) ≦159 160-219 220+
20 *Oleic acid* (in grams per week) ≦179 180-239 240+
21 *Linoleic acid* (in grams per week) ≦99 100 159 160+
22 *Total carbohydrate* (in grams per week) ≦2 199 2 200-2 799 2 800+
23 *Carbohydrate from starch* (in grams per week) ≦1 399 1 400-1 999 2 000+
24 *Eggs* (in calories per week) ≦299 300-499 500+
25 *Bread* (in calories per week) ≦3 999 4 000-6 999 7 000+
26 *Potatoes* (in calories per week) ≦299 300-699 700+
27 *Rice* (in calories per week) ≦199 200-599 600+
28 *Cereal* (in calories per week) ≦199 200-399 400+
29 *Total calories* (per week) ≦15 999 16 000-20 999 21 000+
30 *Per cent of calories from saturated fat* ≦9 10-12 13+
31 *Ratio of linoleic to saturated fat* ≦0 39 0 40-0 69 0 70+
32 *Ratio of saturated to unsaturated fat* ≦0 54 0 55 0 74 0 75+
33 *Ratio of linoleic to total fat* ≦0 33 0 34 0 35 0 36+
34 *Ratio of oleic to total fat* ≦0 15 0 16-0 21 0 22+
35 *Ratio of saturated to total fat* ≦0 31 0 32 0 37 0 38+

Dietary salt We wanted to obtain data on this variable but were unsuccessful in our efforts at quantification For example subjects were able to indicate how many eggs they usually ate per week but were not able to quantify for us how much salt was consumed with them

36 *Marital status* Divorced widowed or bachelor married once married more than once
37 *Occupation* Administrative professional technical laborer
38 *Subject s education* Elementary or less partial or full high school higher education
39 *Wife s education* Elementary or less partial or full high school higher education
40 *Wife s occupation* Housewife additional work at home works outside the home
41 *Hours per week of wife s outside work* ≦19 20-39 40+
42 *History of heart attack* (verified by survey staff from hospital or other medical records) No yes
43 *History of peptic ulcer* (partially verified by survey staff) No yes
44 *Angina pectoris* Negative suspect definite
45 *Intermittent claudication* No yes
46 *Cigarette smoking* (excluding ex smokers) Never 1 10 11 20 20+
47 *Pulse rate* (per minute) ≦70 71 90 91+
48 *Peripheral arterial disease* Negative suspect definite
49 *Emotional state* (the number of positive answers to the questions— Do you consider yourself a tense person? Do you generally suffer from anxiety? Do you generally suffer from sleep problems [insomnia]?) 0 1 2 3
50 *Past financial trouble* None (low) not serious serious very serious (high)

A test at ne xam ce ter showed o re cent bad ra Lo- gr rhic idence f per l ef

or of their muffling in cases in which they did not disappear. This blood pressure was then recorded and the physical examination carried out. At the end of the examination and before blood taking, the blood pressure was measured a second time, approximately 15 to 30 minutes after the first, using the same method. The second measurement*, considered to be closer to a near basal pressure, has been used in the present paper. Methods related to quality control have been reported previously[4].

There are many possible ways of investigating blood pressure changes or incidence of hypertension and they revolve around the question of definitions of hypertension, who are the persons at risk, the variability of blood pressure estimations, and so on. The WHO has defined hypertension as readings at or above 160 mm Hg systolic and 95 mm Hg diastolic. The major objection to this definition is that it does not take age into consideration. While this is reasonable for use among communities where blood pressure does not rise with age, its value may be limited for those areas where it does. What clinician would designate a 70 year old man with a blood pressure of 162/97 as a hypertensive? On the other hand, one might adopt figures which in all circumstances and ages would be agreed as being hypertensive, e.g. a reading higher than 180/100. However, whereas the latter is more specific, it would exclude many cases which clinically would be included as hypertension. A compromise might be adopted by defining hypertension as the upper 10 or 15 per cent of each age group by their blood pressure level, which would thus vary by age. However this would tend to artificially equate incidence rates for all age groups.

The above definitions all depend on a specified level of pressure which in itself is questionable. A further technique therefore might be to measure the change in blood pressure from the last reading to the first. Here again there are problems, as the amount of change is partly a function of the initial reading. The latter also influences the question of who is at risk when using specified levels to define disease because obviously those initially nearest to the level specified will have more chance of crossing the critical point and being labelled as hypertensive.

As no one method appears to be the ideal one, we report here on incidence using the WHO definition and hope that in the future we shall be in a position to use some of the other methods and compare the results.

In this paper our interest is focused on individual rather than group changes and we have accordingly designated as at risk for hypertension incidence all individuals with 1963 blood pressures less than 140 mm Hg systolic *and* less than 90 mm Hg diastolic. As incidence cases we count those individuals who are found on subsequent examination to have pressures of 160 or more systolic *and* 95 or more diastolic in keeping with levels recommended by WHO[3]. More exactly, those at risk in 1963 were counted as incidence cases if found to have 160/95 or more in 1968 or 160/95 or more in 1965 with the 1968 reading above the 139/89 levels or unknown. Those with both 1965 and 1968 readings unknown were removed from the population at risk reported herein.

Of the 10 059 men examined in 1963, 95.3 per cent were examined again in 1968. An additional 2.8 per cent had died in the five year interval. Only 1.9 per cent were lost[illegible].

An itemization of the variables reported in this paper other than age, area of birth and blood pressure is given below. For continuous variables the association with incidence of hypertension was calculated for the lower, middle and upper third of the variable. Since these cutting points were determined for the total population in the study, they are only approximately equal thirds for those at risk for incidence of hypertension. The cutting points for continuous variables as well as the 2, 3, 4 or 5 groupings studied for other variables are specified. Detailed description of data collection for many of the variables listed can be found in previous reports[5, 6], but because of its complexity we insert at this point an outline of the dietary data collection procedures. During a twenty minute interview conducted by specially trained

*In the 1965 examination only one measurement was made at a point in the examination equivalent to the second measurement on the 1963 and 1968 examinations.

period 1963 1968

Area of birth†	No at risk	Incidence per thousand (age-adjusted)	
		Five year	Approximate annual
Israel	566	37	7
Eastern Europe	683	61	13
Central Europe	511	63	13
Southern Europe	606	76	15
Asia	953	51	10
Africa	510	28	6
Total	3 839	51	10

In investigating the relationships of many variables to the risk of developing hypertension as defined we have calculated hypertensive incidence rates (adjusted* for age and area of birth by the direct method to the total study population) for each of the classes designated in the Methods section Both for numeric variables (such as No 5—weight/height ratio where the approximate tertiles were coded 1 2 3) and for coded variables with a clear ordering or direction (such as No 50—past financial trouble where the codes for none not serious serious and very serious were designated 1 2 3 4 respectively) we calculated the slope of the incidence rates on the independent variable the standard error of the slope and the resultant t value For other non numeric variables where the ordering of classes had no directional sense to it (such as No 63—trying to improve job where the classifications are certain to succeed not certain to succeed not trying because no chance to succeed and not trying satisfied with present job) we calculated χ^2 for a 2 × N contingency table

No effort has been made to distinguish or to separate cases of secondary hypertension The incidence cases reported herein are a mixture of essential and secondary cases

Results

The incidence of hypertension (160 systolic or over *and* 95 diastolic or over) is shown in Table I by age group and by area of birth Although there is an opinion to the effect that new cases of essential hypertension are rare after age 50[9] we find otherwise On the assumption that our incidence cases like other groups reported are about 90 per cent essential and only about 10 per cent secondary cases[10,11] the present data suggest that incidence of essential disease increases with age within the age span of a working population The age adjusted five year incidence rates for the area of birth groups vary from a low of 28 per 1 000 for those born in Africa to a high of 76 per 1 000 for those born in Southern Europe The three area groups with the highest rates were the three groups of men born in Europe

*Th[illegible] e so f [illegible] dj[illegible] t g rat[illegible] rem[illegible] th[illegible] fl[illegible] ce of [illegible] nd [illegible] a d ff r ce [illegible] abl of nt r t F [illegible] ex m[illegible] suppose th[illegible] e wh[illegible] yield d b orr [illegible] sult on gl[illegible] ose t lera ce t st (GTT) w re m[illegible] h of [illegible] th[illegible] those [illegible] d ca[illegible] l diabetes. Th[illegible] lti g hypert[illegible] i c[illegible] ce [illegible] te f[illegible] the group [illegible] h the [illegible] b [illegible] mal GTT wo ld be higher [illegible] st beca se [illegible] f th[illegible] ld [illegible] g) th[illegible] t[illegible] te f [illegible] [illegible] rmal [illegible] *f the GTT w[illegible] re lat d t hyp t[illegible] on[illegible] we d[illegible]* To e[illegible] thi[illegible] unw[illegible] ted ffect the dj[illegible] ed [illegible] calcul ted a [illegible] f th[illegible] se w th[illegible] b[illegible] rmal gl cose t l[illegible] ce had the sam[illegible] p[illegible] port o[illegible] f old[illegible] perso[illegible] th[illegible] normal The sam[illegible] principle [illegible] p[illegible] l[illegible] to area of b[illegible] th F[illegible] ag[illegible] nd [illegible] d[illegible] ted ra[illegible] [illegible] di[illegible] tm[illegible] t[illegible] based o[illegible] ry [illegible] p[illegible] [illegible] those w th d[illegible] bet[illegible] those w[illegible] hout diabet[illegible] bei[illegible] g [illegible] ss med t[illegible] h[illegible] the sa me p opo t[illegible] [illegible] f ind[illegible] dual [illegible] f [illegible] m[illegible] h[illegible] ge [illegible] d[illegible] [illegible] g 40 to 49 [illegible] m Ea[illegible] rn Eu[illegible] pe) [illegible] e[illegible] ry othe[illegible] subd[illegible] s[illegible] n w thi[illegible] th[illegible] variabl[illegible] be [illegible] g[illegible] t[illegible] ded

Table I. Age and area adjusted incidence of hypertension per 1,000 at risk in the five year

Age in 1963	No at risk	Incidence per thousand (area adjusted)*	
		Five year	Approximate annual
40 49	2 493	39	8
50 59	1 133	61	13
60+	203	102	20
Total	3 829	51	10

*For age differences the probability that the slope of these rates arose simply on a chance basis is <0 001
†For area differences P (χ^2) due to chance is <0 01

51 *Present financial trouble* None not serious serious very serious
52 *Past family conflict* None not serious serious very serious
53 *Present family conflict* None not serious serious very serious
54 *Conflict with wife (keep to self)* Always show outwardly (low) usually show outwardly usually keep it to myself always keep it to myself (high)
55 *Hurt by family (brood)* Usually forget tend to forget tend to brood usually brood
56 *Hurt by family (retaliate)* Very often sometimes seldom never
57 *Hurt by family (restrain retaliation)* Very often sometimes seldom never
58 *Does wife show her love* Very often seldom not enough never doesn t love me
59 *Family listens to you* Always usually sometimes never
60 *Affected by family not listening* Never happens not affected little upset very upset
61 *Past work problems* None not serious serious many serious
62 *Present work problems* None not serious serious many serious
63 *Trying to improve job* Certain to succeed not certain to succeed not trying because no chance to succeed not trying satisfied with present job
64 *Co-workers show they like you* Very often sometimes not as much as I would like never do not like me
65 *Superiors show appreciation* Very often sometimes not as much as I would like never do not like me
66 *Past problems with co workers* None not serious serious many serious
67 *Present problems with co workers* None not serious serious many serious
68 *Past problems with superiors* None not serious serious many serious
69 *Present problems with superiors* None not serious serious many serious
70 *Hurt by co workers (brood)* Usually forget (low) tend to forget tend to brood usually brood (high)
71 *Hurt by superiors (brood)* Usually forget (low) tend to forget tend to brood usually brood (high)
72 *Hurt by co-workers (retaliate)* Very often sometimes seldom never
73 *Hurt by superiors (retaliate)* Very often sometimes seldom never
74 *Hurt by co workers (restrain retaliation)* never seldom usually always
75 *Hurt by superiors (restrain retaliation)* Never (low) seldom usually always (high)
76 *Consider self a closed person* Often talk sometimes talk generally yes yes
77 *Problems in attaining desired living standard* None some many very many
78 *Fight injustice* Never seen or not personally affected cannot do anything yes
79 *Blood glucose* (in milligrams per cent) ≤129 130 159 160+
80 *On diet* No ulcer diet weight loss fat reduction heart disease or high blood pressure
81 *After meal activity* Work mixture of work and rest rest only
82 *Computer ECG infarct* Negative possible myocardial infarction (MI) probable MI
83 *Computer ECG ischemia* No yes
84 *Computer ECG arrhythmia* No yes
85 *Computer ECG conduction defect* Negative right bundle branch block (RBBB) left bundle branch block (LBBB) other
86 *Computer ECG LVH* Negative, possible probable
87 *Computer ECG NST* No yes
88 *Computer ECG left axis deviation* No yes
89 *Computer ECG summary* Negative nonspecific T wave (NST) for ischemia possible MI probable MI or LBBB
90 *Diabetes* No abnormal glucose tolerance test yes

Table II *Five year age and area adjusted hypertension incidence rates for variables* significantly (P < 0 01) associated with hypertension incidence*

Numeric variables (in three classes)	*Five year incidence rates per thousand* — *Low*	*Middle*		*High*	*Slope of incidence rates divided by the estimated standard error of the slope (t value)*
Number of persons living together	63 (1 087)†	56 (1 033)		40 (1 691)	−2 78
Weight/height ratio	29 (1 274)	51 (1 574)		95 (1 020)	6 18
Triceps skinfold	45 (1 243)	51 (1 197)		77 (1 143)	2 85
Subscapular skinfold‡	33 (1 523)	55 (191)		71 (1 988)	4 91
Uric acid	39 (1 741)	71 (873)		69 (1 163)	3 66
Pulse rate§	39 (1 457)	62 (2 187)		113 (174)	4 30
Ordered variables (in four classes)	*Low*	*Middle*		*High*	
Cigarette smoking	41 (1 124)	43 (556)	57 (706)	66 (873)	2 60
Hurt by superior (brood)	54 (954)	43 (987)	72 (670)	76 (830)	2 60
Hurt by superior (restrain retaliation)	35 (410)	63 (814)	58 (1 570)	81 (667)	2 58

*See Methods section for full description of classes for each variable
†Number of persons at risk on which rates are based
‡A more reasonable division of classes ... this variable and as a result there are very few cases in the middle third
§Was deliberately broken by rule of tertiles for this variable ... to each level of 91+ for the upper third

to detect true associations we have no reason to believe that our failures to find significant associations are necessarily similar to what we would have observed if we had been able to study hypertension rather than casual blood pressure readings As a consequence we have a greater sense of security with respect to our findings of a significant association than we do with respect to our failure to observe a significant association Accordingly our comments and comparisons with other reports in the literature are restricted to those variables which we find significantly associated with hypertension incidence

The area of birth differences in observed incidence rates are similar in a gross way to those observed for incidence of myocardial infarction[1] in that none of the three European groups had lower rates than the Asian African or Israeli groups However the area differences with respect to hypertension incidence are much greater than they are with respect to myocardial infarction (MI) The ratio of highest to lowest five year rates for MI is 1 35 (Central Europe 0 050/Asia [except Israel] 0 037) but 2 71 (Southern Europe 0 076/Africa 0 028) for hypertension Undoubtedly some of the greater variability in area incidence rates for hypertension reflects the smaller number of cases observed in the population at risk Making allowance for the fact that we had no prior hypothesis that Southern Europe would be highest and Africa lowest for hypertension incidence this ratio is not significantly different from unity at the p <0 01 level In view of the fact that the mean blood pressure values among areas did not differ significantly[13] we reserve judgment as to whether area differences in hypertension incidence are really so disparate as our raw data suggest The finding that those born in Europe have higher hypertension incidence rates than those born in Israel elsewhere in Asia or in Africa is probably a real finding even though we presently lack a sense of the true size of the differential Taken together with the similar finding about MI it opens an area for study as to factors present in these two groups that may explain the difference in incidence Multivariate analyses of our data now in prog

In Table II are presented the five year age area adjusted incidence rates for specific levels of the nine variables found to be significantly associated with incidence of hypertension Among the ninety variables listed in the "Methods" section only these nine were associated with incidence to the degree that would be observed by chance alone less than one time in a hundred The variables are No 3—number of persons living together No 5—weight/height ratio, No 6—triceps skinfold No 7—subscapular skinfold No 12—uric acid No 47—pulse rate No 46—cigarette smoking, No 71—hurt by superior (brood) and No 75—hurt by superior (restrain retaliation) All of these variables are subject to logical ordering and we have therefore calculated a weighted least squares regression coefficient* relating the hypertension incidence rate to a simple scale 1 2 3 or 1 2 3 4 for the independent variable All of the relationships in Table II are positive except for variable No 3 where the highest incidence rate was associated with the smallest size group of persons living together

Because we are investigating so many variables we are concerned about the problem created by multiple significance tests where it becomes almost a certainty that something will be significant To minimize the difficulties we have reported above and will consider in the discussion section to follow only those variables significant at $p < 0.01$ The variables associated with hypertension incidence for which the significance level is between 0.01 and 0.05 may simply be reflecting chance associations and unless these have previously been reported in other studies we refrain from commenting on them They are listed below for the record so that subsequent incidence studies may note whether their association with hypertension is replicated To the extent that they are it would be profitable and desirable to then return these variables for further analysis T[illegible] variables in the significance range $p = 0$[illegible] to $p < 0.05$ are No 1—year of immigrati[on] (longest residents tend to have highest in[ci]dence rates), No 4—number of rooms (n[eg]ative association), No 8—serum cholest[e]rol No 19—saturated fat (negative asso[ci]ation), No 30—per cent of total calor[ies] from saturated fat (negative associatio[n]) No 38—subject s education No 51—pr[es]ent financial troubles (negative associatio[n]) No 54—conflict with wife (keep to se[lf]) No 63—trying to improve job No [illegible] hurt by co workers (brood), No 87—n[on]specific T wave One other association [we] wish to mention is that for No 1[illegible] hematocrit Its relationship to blood pr[es]sure incidence is clearly "U" shaped t[hat] is, both low and high values of hematoc[rit] are associated with increased risk but [we] had no prior hypothesis* to this effect a[nd] therefore make no comment as to its [sig]nificance

Discussion

At the outset it is important to emp[ha]size that "incidence of hypertension[ ] used in the title and elsewhere in this pa[per] with reference to our study actually me[ans] incidence of elevated blood pressure [We] are inclined to believe that the associati[ons] found with elevated blood pressure in[ci]dence would also be found with es[s]en[tial] hypertension in this population if it [had] been operationally feasible to define [the] latter in terms of blood pressure le[vels] always or almost always above the 160 level Because of the obviously greater [im]pact of measurement error in a sin[gle] reading and the consequent loss of po[wer]

*For each of the three or four values of the variables being studied we have calculated an age adjusted [illegible] incidence rate If there were no relationship between this variable and hypertension incidence the slope of these incidence rates could be expected to be zero The weighted least squares regression coefficient is the slope calculated under ordinary statistical formula but with [illegible] weight given to those incidence rates based on larger numbers of subjects and less to those based on a smaller number

*Any moderately large body of data can be found to d[isclose] some unusual feature due to chance alone Unless [the] unusual [illegible] is consistent with a priori hyp[othesis] it is better to interpret it cautiously or to withhold judg[ment] [illegible] rather than one of critical discovery Th[is] case with our finding of a "U" shaped association bet[ween] hematocrit and blood pressure incidence Among [illegible] blood unusual features of hematocrit levels [illegible] those with hematocrit of each [illegible] may be shown on unusually high incidence rate [illegible] with the [illegible] [illegible] Thousands of unusual [illegible] could be specified We [illegible] that one or more of these unspecified and expected events has in fact happened

Table III Age specific and age and area adjusted five year hypertension incidence rates per 1000 in relation to number of persons living together and number of children

Age	No of persons living together			Slope of incidence rates divided by the estimated standard error of the slope (t value)
	1 3	4	5 9	
40-49	48	45	30	−1 95
50-59	69	94	49	−1 07
60+	143	37	57	−1 73
Total	63	56	40	−2 78

Age	No of children			Slope of incidence rates divided by the estimated standard error of the slope (t value)
	0 1	2 3	4 9	
40-49	51	40	28	−2 07
50-59	76	72	57	−0 96
60+	93	119	125	0 54
Total	60	56	53	−0 66

of this association include cross sectional data from Framingham[26] and a report that patients with gout tend to develop renal insufficiency and hypertension[27] although after histological studies of renal biopsy tissue in hypertensives with gout and hypertensive patients without gout the latter report concludes that there is no evidence to explain the propensity of gouty individuals to develop hypertension

In reporting the association between pulse rate and systolic blood pressure found in cross-sectional data from this study[12] it was not certain whether or not the association reflected a mechanical increase in pressure when the pump was operating at a higher rate The present data suggest that something more fundamental may be involved Recent reports on this association include one on the cross sectional relationship in human beings[28] one on the cross sectional relationship in rats[29] and a plea to regularly include pulse rate as a variable for analysis in future blood pressure studies[30]

The positive association we find between cigarette smoking and hypertension incidence contributes another fact to an area clouded by contrary findings Large prospective studies of mortality risk have reported an excess number of deaths from hypertension and/or hypertensive heart disease among cigarette smokers[31 32] while it is not uncommon for cross sectional studies to find no relation between cigarette smoking and blood pressure[24 34] Possible but by no means necessary conclusions to be drawn from these facts are that (1) case fatality associated with hypertension and its sequelae among smokers may be high enough to obscure this relationship in cross sectional studies and (2) cross sectional studies may be recording smoking habits which have changed after disease onset

It is now about 40 years since the first systematic studies of the relationship between personality and/or sociocultural factors to hypertension were reported Many of these studies were based on small numbers of clinical cases case control studies and other retrospective investigations after the onset of hypertension The difficulties and problems of these have been detailed in a review of the field[35] Most of the studies found some differences between hypertensives and nonhypertensives although two studies were unable to demon

ress, may help to shed some light on this matter

We found one report which could reasonably be compared with our data as to level of incidence. This was derived from periodic health examinations offered by companies in the United States of America to their male employees.[14] With those at risk defined as under 130 systolic, annual rates per 1,000 of 160 systolic or over *or* 95 diastolic or over *or* "stated diagnosis (of hypertension) in the medical record" were 5.7, 10.9, and 16.8 for ages 30 to 39, 40 to 49, and 50 to 59. Our five year incidence rates divided by five for rough approximation to annual rates are 7.8 for ages 40 to 49 and 12.8 for 50 to 59. With our group at risk defined to be under 140 (tendency to give us higher rates) and our incidence cases defined as 160+ *and* 95+ (tendency to give us lower rates), it is difficult to say any more about this comparison than that the figures are of the same order of magnitude. Apart from level of rates, we note that our data confirm the finding from periodic health examinations that incidence rates go up with age in this age range.

Other reports on incidence of hypertension[15-20] were not comparable with our data, principally because of failure to provide age specific information or because persons with pressures just barely below the definition of hypertensive level were included in the population at risk.

Our finding of an inverse relationship between incidence of hypertension and "number of persons living together" is consistent with earlier reports for males indicating an inverse relationship between average blood pressure and number of children[1] and prevalence of hypertension and number of children.[22] Curiously enough, our own data relating number of children to hypertension incidence revealed no over-all significant association. Looking at the data on number of children for specific age groups, however, showed that there was a significant negative association ($p < 0.05$) for age 40 to 49, a negative association but not strong enough to be significant at age 50 to 59 and a weak positive association at age 60+. These data together with the age specific data for number of persons living together are summarized in Table III. The data are consistent with the hypothesis that the association is in fact with the size of the household rather than with the number of children. Evidently the other studies showed an association with number of children because the ages of their subjects as reported were substantially younger than ours. At younger ages the correlation between number of children and number of persons presently in the household is presumably much stronger than at older ages. On this basis, we can speculate that there is something in the interactions among many persons living closely together* that is inimical to the development of high blood pressure among males of the age groups in our study. It is also of some interest to note that in our study of the incidence of myocardial infarction we have also found a negative association with the number of persons living together.

As in our study, relative body weight and skinfold measurements have often been reported as positively related to hypertension.[14,16,23,24] The judgment that the artifact of thick arms is only partly responsible for the association of blood pressure and obesity[25] is strongly supported by our incidence data which relate to measures of obesity and body size in a population entirely free of hypertension at the time of measurement. Looking at Table II we observe that both the weight/height ratio and the subscapular skinfold measurement are strongly related to hypertension incidence. The association with triceps skinfold is also positive and significant at the $p < 0.01$ level but is not nearly as strong as that for the other two measures of body size. Perhaps part of the explanation for this difference may be in the greater difficulty and hence greater measurement error in the determinations of the triceps skinfold in comparison to weight/height or the subscapular skinfold.

The finding of a significant association between systolic blood pressure and serum uric acid level in our 1963 cross-section examination[13] is confirmed and somewhat clarified by our present finding of a significant association between uric acid and incidence of hypertension. Previous report

*This association is with the actual number of people living together but is not related to the crowding index (No. 15—number of persons per room).

he development of hypertensive levels is more probable for those with blood pressures at the upper boundary of normal and less probable for those with pressures much below this In the present paper we have established some associations between certain variables and subsequent hypertension incidence In later reports from this study using multivariate methods we hope to explore whether the variables we have identified contribute to excess risk only through their association with base line pressure or whether there is a significant association after an adjustment for base line pressure is made In any event we are presently only at the beginning of our understanding of the relationship between hypertension incidence and the variables considered herein

Summary

In a study of male Israeli civil service workers five year incidence rates of hypertension (using the WHO definition) were found to increase with age and were higher for European born subjects Data are presented in support of a hypothesis that the size of the family group living together is inversely related to the risk of developing hypertension Other factors found associated (at $p < 0.01$ level) with hypertension incidence (all positively) were weight/height ratio skinfolds serum uric acid pulse rate cigarette smoking and prolongation and suppression of feelings following conflicts in certain life situations Other associated variables between the <0.01 and <0.05 levels are recorded and the fact is stressed that we are only at the beginning of an understanding of factors associated with hypertension incidence

Our sincere thanks go to Prof J J Groen for much of the thinking and the development of the questionnaire related to the psycho-social variable used in this study

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strate this.[3,38] In our initial survey we adopted the procedure of asking whether the subject had presently or in the past, any serious problems in a number of life areas and how he had responded to them. This in essence defines a category which is resultant of the interaction and interrelation between the personality and the sociocultural situation without at this stage trying to differentiate the effects of each. In addition we developed an anxiety index based on the sum of the answers to a number of questions.

Leaving out of the discussion at this stage the psychosocial aspects of biological variables like cholesterol, uric acid, weight, and so on, significant associations were found with six psychosocial variables. Of these, four of them 'hurt by superior (brood)', 'hurt by superior (restrain from retaliation)', 'hurt by co-workers (brood)' and 'conflict with wife (keep to self)' have a common denominator in that they represent a conflict situation with the subject restraining or repressing his feelings within himself in line with parts of the hypotheses as set out by various psychiatrists and others.[39,40] At this stage we have no evidence that this reflects 'an inability to utilize previously socially sanctioned patterns of behavior,' as suggested.[41]

This present paper is limited to the relationship between hypertension incidence and various single variables of interest with the investigation of multivariate relationships to be reported later. However because the present findings of significant relationship include cigarette smoking, some manifestations of psychic tension and the number of persons living together and because it is not unreasonable to suppose that tense people may smoke heavily and be 'loners', we have investigated the correlation of these variables in our data. For the present, it seems as if each of the three variables cited above is in fact independently related to hypertension incidence. However more intensive and precise multivariate investigations are in process and will be reported at a later date.

With respect to those variables that we found significantly associated with hypertension incidence at the 0.05 level, we note that the negative relationship with education has been previously reported in cross-sectional studies from the Framingha Study[4] and the National Health Survey.[?] The positive associations between non-specific T wave and blood pressure lev and cholesterol and blood pressure leve have been previously reported from Fram ingham.[4,6]

A rough over-all comparison of findings between our cross-sectional study of bloo pressure in relation to specific variables and the present study shows (for variabl included in both studies): (1) five variabl with similar relationships to blood pre sure level or hypertension incidence: a weight/height ratio, uric acid, pulse rat and cholesterol; (2) five variables s nificantly associated with blood pres in the cross-sectional study but not wi hypertension incidence: myocardial i chemia, anxiety index, diabetes, angir and peptic ulcer history (negative); (three variables significantly associated wi hypertension incidence but not with cro sectional blood pressure values: number persons living together, years in the co try and education; and (4) one variabl significantly associated with blood pressu level in the cross-sectional study (negat association) and significantly associa with hypertension incidence in the pr ent study (positive association): cigare smoking.

This is not an appropriate place to d cuss in depth the comparative findi with respect to the same variables prevalence (cross-sectional) and incide studies but a few remarks may be app priate. (1) Of the nine associations fou in the incidence study five were also ide fied in the prevalence study. (2) The as ciations found in the cross-sectional stu but not in the prospective incide analysis are mostly with morbid co tions. (3) The distortion potential o cross-sectional prevalence study is gr enough to invert an association from which in fact is probably positive t finding of negative.

We are aware of the fact that in relat variables to future development of hyp tension we may in effect be doing no m than relating these variables to blood p sure levels *within* the population defi to be at risk of hypertension. This foll since among those at risk it is evident t

Interrelationship of hemodynamic alterations of valvular heart disease and renal function

Influences on renal sodium reabsorption

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Definition of the mechanisms responsible for the abnormal salt and water retention which characterize congestive heart failure remains a challenging problem to clinical investigators despite the remarkable conceptual advances of the last 30 years. Stimulated by the elegant studies of Starr[1] which led to the formulation of the forward theory of heart failure, Warren and Stead[2] demonstrated a diminished urinary excretion of sodium and water in cardiac patients commensurate with edema formation. Their findings were confirmed and extended by Merrill[3] and by other investigators[4,5,6] who showed that renal plasma flow and glomerular filtration rate were reduced in patients with heart failure leading to speculation that the abnormal salt and water retention simply reflected a more complete tubular reabsorption of the diminished filtered load of sodium. However, several disparities were reported which could not be easily explained by this proposed mechanism. These included (1) evidence that renal sodium retention occurred in dogs with experimental heart failure before any measurable decrease in glomerular filtration rate was recorded,[7] (2) the development of heart failure in human subjects with normal glomerular filtration rates,[8,9] and (3) spontaneous or induced diuresis during compensation of heart failure without concomitant improvement in depressed glomerular filtration rate.[10,11] Despite these inconsistencies, Vander and associates[12] in

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Table I Clinical summary of 19 patients studied during cardiac catheterization

No. of patients	Sex M	Sex F	Diagnosis	Functional class*	Average age (yr.)
10			Mitral stenosis and/or insufficiency		37.3 ± [illegible].8
3			Aortic stenosis and/or insufficiency		
4			Mixed mitral and aortic valve lesions		
1			Ostium primum defect		
1			Left atrial myxoma		
5				Class I	
6				Class II	
8				Class III	
	3	16			

*According to the New York Heart Association classification.

for mixed venous blood sampling. Systemic arterial blood samples were obtained from an indwelling polyethylene catheter placed percutaneously in the left brachial artery. A cardiac catheter with a preformed curved tip was inserted percutaneously in the right femoral vein and the catheter tip was positioned in the right renal vein for blood sampling. Urine specimens were obtained from an indwelling urethral catheter.

Inulin and para-aminohippuric acid (PAH) clearance were measured using a constant infusion technique. Priming doses of PAH (0.03 ml. of 20 per cent PAH per kilogram of body weight) and of Inulin (0.5 ml. of 10 per cent Inulin per kilogram of body weight) were given initially; these were followed by a constant intravenous infusion of a solution containing 50 ml. of 10 per cent Inulin and 10 ml. of 20 per cent PAH in 500 ml. of 5 per cent dextrose in water delivered by an Amedeco pump at a rate of 3 ml. per minute. At this infusion rate the plasma concentration of PAH remained below 5 mg. per cent in all patients. The infusion was continued for at least 45 minutes before the study period to allow establishment of an equilibrium state; during this time catheters were inserted as indicated above. The patient was then allowed to enter a resting state and urine was collected during two sampling periods of 20 minutes each. The urinary bladder was irrigated with sterile distilled water and emptied at the beginning of the first collection period, then emptied and irrigated with a known volume of distilled water at the end of each collection period to insure accurate sampling. Brachial arterial and renal venous blood samples were drawn at the beginning and end of each collection period. Cardiac output was measured by the Fick method at the midpoint of the first collection period and by the radioisotope dilution technique with precordial detection midway through the second period; intravascular pressures were recorded at both times. Satisfactory positioning of the catheter in the renal vein was verified at the beginning and end of the study by injection of a small amount of radiographic contrast material and by oximetry of renal vein and inferior vena cava blood samples demonstrating high oxygen saturation of the former.

The methods used to analyze the PAH

1958 rejuvenated interest in the abnormal filtration fraction which characterizes the renal perfusion/filtration adjustment in heart failure.[12] They suggested that blood perfusing the proximal tubule in congestive heart failure had a higher plasma protein concentration because of the increased filtration fraction, resulting in an increased colloidal osmotic pressure favoring passive sodium and water reabsorption from the proximal tubule into the peritubular capillary network.

The lack of a consistent relationship between filtered load of sodium and diminished urinary excretion prompted other investigators to search for alternate or supplementary factors which might operate independently or in concert with altered renal perfusion/filtration to cause abnormal salt and water retention. Excretion of aldosterone, a potent endogenous mineralocorticoid, was found to be increased in patients with congestive heart failure, suggesting the possibility that the increased tubular reabsorption of sodium present in heart failure may be the result of increased aldosterone activity.[13] Sufficient data have accumulated to recognize aldosterone overproduction as a significant factor both in perpetuating and in augmenting the pathologic sodium retention of heart failure.[14,15] However, the absence of edema in patients with primary aldosteronism and the induction of experimental heart failure in adrenalectomized dogs maintained with minimally effective concentrations of exogenous mineralocorticoid replacement[16] precluded increased aldosterone production as the primary salt retaining mechanism responsible for sodium retention in congestive heart failure.

Theories concerning renal regulation of sodium excretion continued to be dominated by consideration of altered filtration rate and aldosterone activity until the early 1960's when two independent observations expanded the number of factors known to modify renal sodium excretion. The first was the finding by deWardner and associates[17] that a sodium diuresis could be induced in dogs despite a severe reduction in glomerular filtration rate and in the presence of excess exogeneous mineralocorticoid by the infusion of hypotonic saline. Confirmation of this discovery by Levinsky and Lalone[18] initiated th[e] search for a "third" factor responsible f[or] the regulation of proximal tubular sodium reabsorption. Findings in support of th[e] regulatory mechanism being humoral in origin[19] and/or physical in character[9] hav[e] been reported to explain the saluresis a[s]sociated with rapid expansion of the extra[-] cellular space. The second major contri[bu]tion was the report by Barger[1] demonstra[t]ing a redistribution of intrarenal blood flow in dogs with experimental heart failure. Using an inert radioactive gas technique he found intrarenal flow to be directed away from superficial cortical nephrons which do not conserve sodium as avidly as the deep cortical and juxtamedullary nephrons to which blood flow is increased in heart failure. These observations have stimulated a reappraisal of the pathophysiologic mechanisms responsible for salt and water retention of heart failure. In the following study we have examined the influence of the systemic and renal hemodynamic alterations of heart failure on renal tubular sodium reabsorption.

Methods

Nineteen patients were studied dur[ing] routine diagnostic cardiac catheterization and were selected to include a spectrum of severity of heart disease. Patient data are tabulated in Table I. Seventeen individuals had valvular heart disease, one had an ostium primum defect, and one had a left atrial myxoma. Applying the New York Heart Association Classification at the time of study, five patients were in Functional Class I, six were in Class II, and eight were in Class III. All patients were free of overt evidence of heart failure when studied, although all of those in Class III and most of those in Class II had previously demonstrated pulmonary and/or systemic venous congestion. Thirteen patients were taking digitalis at the time of study, and eigh[t] were following a sodium restrictive diet of 2 Gm. or less per day. Five patients ha[d] been taking thiazide diuretics prior t[o] hospitalization but these were discontinue[d] at least 2 days prior to study.

Right heart catheterization was carrie[d] out by standard techniques from a righ[t] antecubital cutdown with positioning [of] the catheter tip in the pulmonary arte[ry]

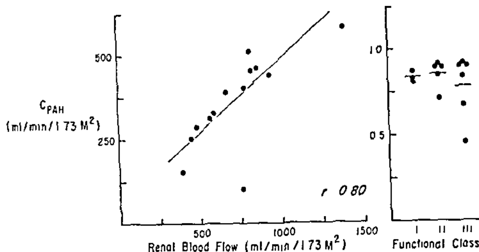


Fig 2 Correlation plot between para aminohippurate clearance (C_{PAH}) and renal blood flow constructed similar to Fig 1 The right hand graph compares the renal extraction ratio of PAH (ordinate) to the functional cardiac class. The horizontal lines represent the mean values for each group of solid circles

of sodium (T_{Na^+}) was obtained as the difference between filtered sodium and total urinary sodium ($F_{Na} - U_{Na}V$) expressed as mEq /min

Results

Comparison of systemic hemodynamic parameters of patients Four hemodynamic variables were compared to cardiac index the classical measure of systemic hemodynamic function These included (1) mean left atrial pressure (2) mean pulmonary artery pressure (3) arteriovenous oxygen difference and (4) total blood volume Fig 1 depicts the inverse correlation between cardiac index and mean left atrial pressure the correlation coefficient (r) of -0.78 was highly significant A similar relationship existed with mean pulmonary artery pressure ($r = -0.68$) As expected because of the interdependence a significant inverse correlation was evident between arteriovenous oxygen difference and cardiac index ($r = -0.82$) No consistent relationship could be demonstrated between cardiac index and total blood volume ($r = -0.30$) Since the determinations of cardiac index and mean left atrial pressure are not interdependent we chose them as hemodynamic parameters for comparison with the measurements of renal hemodynamics

Extraction of PAH It has been suggested[4] that the extraction of para aminohippurate by the kidney declines in patients with congestive heart failure thus distorting the expected linear relationship between renal blood flow and C_{PAH} In 15 of the 19 patients studied it was possible to obtain a technically satisfactory renal vein blood sample for PAH analysis To determine if clearance of PAH was a true reflection of renal blood flow the clearance of PAH was compared to renal blood flow corrected for both hematocrit and extraction ratio of PAH An excellent correlation existed between these two parameters (Fig 2) and no consistent relationship between E_{PAH} and cardiac functional classification was evident We have concluded that C_{PAH} is a reliable estimate of renal blood flow under the conditions in which our patients were studied

Comparison of systemic and renal hemodynamics Relationships between systemic hemodynamic variables and C_{PAH} are shown in Fig 3 In confirmation of the recent report of Kinoshita[2] there was a significant direct correlation between cardiac index and PAH clearance ($r = 0.75$) As would be expected from the hemodynamic relationships above C_{PAH} correlated inversely with mean left atrial pressure and had no relationship to total blood volume

Filtration fraction the portion of renal plasma flow filtered by the glomerulus had

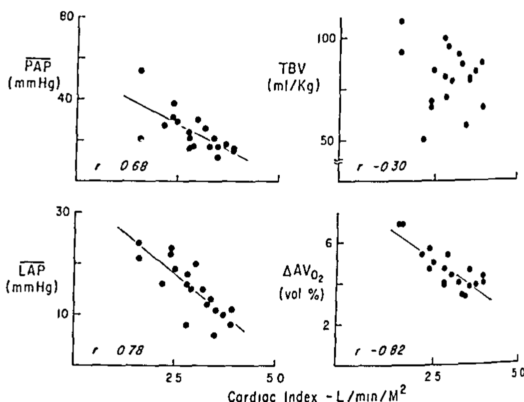


Fig. 1. Four correlation plots comparing cardiac index on the abscissa to various hemodynamic parameters on the ordinate. $\overline{LAP}$ = mean left atrial pressure, $\overline{PAP}$ = mean pulmonary artery pressure, AV_{O_2} = arteriovenous oxygen difference, TBV = total blood volume. Regression lines were obtained by the method of least squares and r represents the derived correlation coefficient (see reference No. 41).

and Inulin content of serum and urine samples were identical to those previously reported by this laboratory. Plasma clearance of PAH was calculated from the formula

$$C_{PAH} = \frac{U_{PAH} \times V}{P_{PAH}} \qquad (1)$$

where U_{PAH} and P_{PAH} represent the urine and plasma concentrations and V represents the volume of urine. The renal extraction of PAH was calculated from the formula

$$E = \frac{A_{PAH} - V_{PAH}}{A_{PAH}} \times 100 \qquad (2)$$

where A_{PAH} and V_{PAH} are the concentrations of PAH in the systemic arterial and renal venous blood. Renal blood flow is calculated from the formula

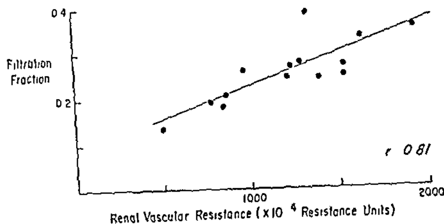
$$RBF = \frac{C_{PAH}}{E_{PAH}} \times \frac{100}{1 - \text{hematocrit}} \qquad (3)$$

Inulin clearance was calculated as with the PAH clearance formula. The brachial arterial and mixed venous blood samples for Fick cardiac output calculation were analyzed for oxygen content by the Van Slyke Neill method and the expired gas sample was analyzed for oxygen content by the Scholander technique. Cardiac output determination by the radioisotope dilution technique was performed as described previously with injection of 1 μCi of ^{131}I labeled human serum albumin in the right atrium.[3] Intravascular pressures were measured with Statham P 23Cb transducers and recorded on a Sanborn photographic recorder.

Renal vascular resistance (RVR) was calculated using the following formula

$$RVR = \overline{BP} - RAP/RBF \qquad (4)$$

where $\overline{BP}$ is mean arterial blood pressure, RAP is right atrial blood pressure, and RBF is renal blood flow corrected for PAH extraction. Vascular resistance was expressed in arbitrary units. Renal oxygen consumption was derived as the product of renal blood flow and renal arteriovenous oxygen difference, the result expressed as ml/min/1.73 M². Tubular reabsorption



5 Correlation plot of filtration fraction (FF) versus renal vascular resistance Constructed similar to Fig 1

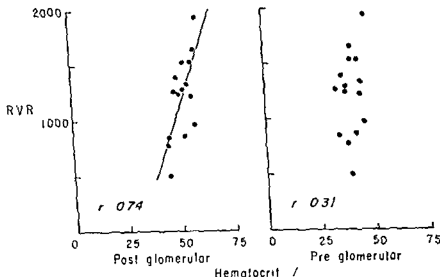


Fig. 6 Correlation plot of renal vascular resistance (RVR) compared to pre and postglomerular hematocrits Constructed similar to Fig 1

patients but the individual values did not correlate with the severity of the impaired cardiac output (Fig 7)

In an attempt to appraise any renal adaptation to decreased cardiac output the renal arteriovenous oxygen difference was compared to the cardiac index A highly significant inverse correlation resulted which was also true when renal blood flow was compared to cardiac output (Fig 8) Thus it would appear that as cardiac output is diminished renal blood flow follows at an equal rate and the renal arteriovenous oxygen difference increased in a manner similar to muscle and other tissues

Comparison between hemodynamic alterations and renal tubular sodium reabsorption It has been suggested that the increased filtration fraction associated with the diminished renal blood flow in patients with heart failure maintains the filtered load of sodium resulting in a relative enhancement of tubular sodium reabsorption In an attempt to elucidate a pathophysiologic mechanism consonant with increased filtration fraction and sodium retention we examined glomerulo tubular balance in our patients When the filtered load of sodium was plotted against net tubular reabsorption of sodium for all 19 patients a near

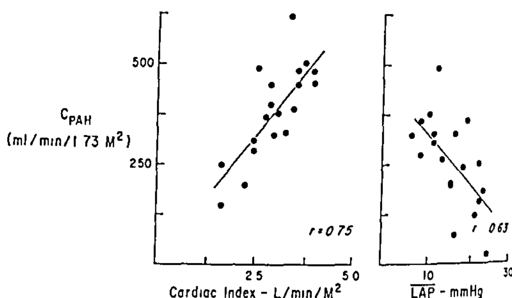


Fig 3 Correlation plot of PAH clearance (ordinate) compared to either cardiac index or mean left atrial pressure ($\overline{LAP}$) constructed similar to Fig 1

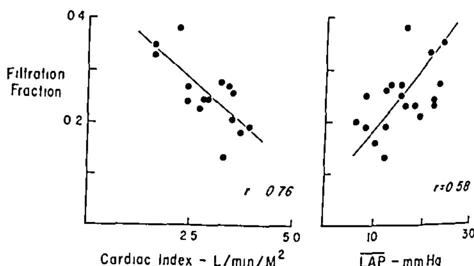
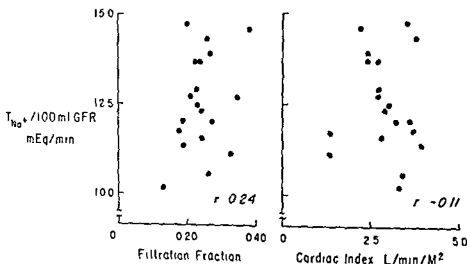


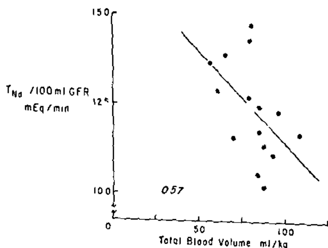
Fig 4 Correlation plot of filtration fraction (FF) (see text for definition) compared to cardiac index or mean left atrial pressure ($\overline{LAP}$) Constructed similar to Fig 1

a highly significant inverse correlation with cardiac index as shown in Fig 4 ($r = 0\ 76$) Previous authors[12] have considered this renal adaptive mechanism to be responsible for the excess Na^+ retention which is characteristic of congestive heart failure From the data presented in Fig 5 it would appear that preservation of the filtration rate in the face of a fall in renal plasma flow occurs through an increase in the efferent or postglomerular arteriolar resistance, since the filtration fraction correlated directly with renal vascular resistance Possibly contributing to the increased resistance is the postglomerular hematocrit, which correlated directly with renal vascular resistance (Fig 6) The possible influence of increased blood viscosity associated with the rising hematocrit on renal vascular resistance has been discussed by Mills[26]

Thus although renal blood flow declines as cardiac index falls there is increased postglomerular vascular resistance which serves to maintain glomerular filtration rate This change in perfusion/filtration balance is not directly dependent on a diminution in the percent of cardiac output received by the kidneys, since the renal fraction averaged 14 6 per cent for our



9 Correlation plot of normalized tubular sodium reabsorption (T_{Na^+}/100 ml GFR) and either filtration fraction or cardiac index Constructed similar to Fig 1



10 Correlation plot of normalized tubular sodium reabsorption and total blood volume Constructed similar to Fig 1

fractional sodium reabsorption from the proximal tubule is the influence of extracellular volume expansion the so called third factor An indirect method for assessing the possible existence of such a modification of tubular sodium reabsorption in our patients is by comparing the normalized tubular reabsorptive rates with simultaneously measured total blood volumes These data are plotted in Fig 10 and demonstrate an inverse relationship between the two parameters Acknowledging that cause and effect cannot be judged from such a correlation plot these findings do support the concept that an alteration in extracellular fluid volume can induce a systematic change in measured tubular sodium reabsorption

Comparison of renal oxygen consumption and tubular sodium reabsorption From various animal studies[28, 29] it has been reported that approximately 30 mEq of sodium are actively reabsorbed for each millimole of oxygen consumed We also measured net sodium reabsorption—that is the difference between the sodium actively transported out of the tubular lumen and that which passively diffuses back into the lumen and we have derived the Na^+/O_2 ratio for each of the patients

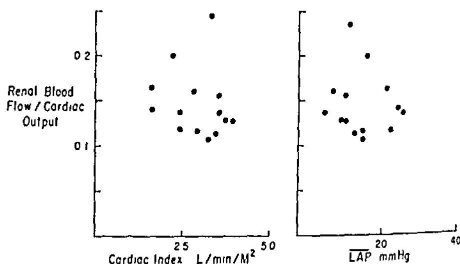


Fig 7 Correlation plot of renal fraction (renal blood flow/cardiac output) compared to either cardiac index or to mean left atrial pressure ($\overline{LAP}$) Constructed similar to Fig 1 See text for statistical analysis.

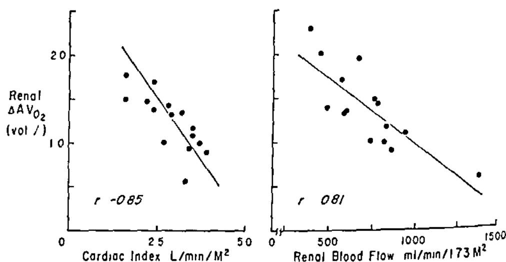


Fig 8 Correlation plot of renal arteriovenous oxygen difference (ΔAV_{O_2}) compared to cardiac index or to renal blood flow Constructed similar to Fig 1

perfect correlation resulted a finding compatible with intact glomerulo tubular balance However since only a minute imbalance would be required to produce appreciable sodium retention this classical technique for expressing glomerulo tubular balance is probably too insensitive to detect the changes which are postulated to occur in congestive heart failure

As an alternate means of detecting a unique enhancement of tubular sodium reabsorption at increased filtration fractions each individual tubular reabsorptive rate was standardized to a common load of 100 ml glomerular filtration rate (GFR) and plotted with respect to the derived filtration fraction These data are shown on Fig 9 In this graph, the normalized tubular reabsorption of sodium appears in the ordinate while either the cardiac output or filtration fraction are shown on the abscissa If in association with an increasing filtration fraction tubular reabsorption of sodium were to increase a linear relationship would be predicted As a corollary if cardiac failure as manifested by a decreased cardiac output were associated with enhanced Na^+ reabsorption then an inverse relationship would exist for cardiac index As can be seen from Fig 9, no significant correlation was present for either filtration fraction or cardiac index This finding supports the conclusion that glomerulo tubular balance is intact in patients with compensated congestive heart failure

Another factor which will modify the

sodium retention both through intrarenal mechanisms that enhance sodium reabsorption and through the secondary effects of the renin angiotensin system to stimulate the secretion of aldosterone. Our findings (Figs 5 and 6) are compatible with such a postulated mechanism. Efferent arteriolar vasoconstriction would result in a lowered capillary hydrostatic pressure perfusing the proximal tubule thus exerting less impedance to sodium reabsorption according to the standing gradient model for sodium transport proposed by Diamond.[35] Furthermore plasma oncotic pressure would rise at an equal rate with the post glomerular hematocrit providing an additional driving force for increased interstitial fluid uptake by the peritubular capillaries. An additional contributing factor would be the slower blood flow in the peritubular capillary network which would provide more time for equilibration thus allowing these physical forces to exert a more complete effect.

A classical plot of filtered load versus tubular reabsorption failed to show any distortion of glomerular tubular balance with regard to renal sodium handling in our patients with heart failure. Obviously minute changes in net sodium reabsorption might be obscured by this type of analysis and still could account for the abnormal salt and water retention of heart failure. To search more critically for the unique tubular enhancement of sodium reabsorption in heart failure postulated above, tubular sodium reabsorption for each patient studied was standardized to a common filtered load and compared to filtration fraction and cardiac index. Since the serum sodium for 17 of the 19 patients was within the normal range for our laboratory and showed no correlation with either filtration fraction or cardiac index only GFR represented a significant variable and it was eliminated by the technique of normalization employed. If associated with an increased filtration fraction elevated plasma oncotic pressure and reduced capillary hydrostatic pressure were primary determinants of tubular sodium reabsorption then a direct relationship with filtration fraction would be expected which was not the case (Fig 9). Conversely if systemic blood flow were to influence T_{Na^+} an inverse correlation would be anticipated and this finding was also absent. These findings support the conclusion that no gross distortion of glomerulo tubular balance exists in patients with compensated congestive heart failure. Further evidence supporting preservation of glomerulo tubular balance is the appropriate response of renal tubular sodium reabsorption to volume expansion as seen in the results presented in Fig 10. The inverse correlation between normalized T_{Na^+} and total blood volume would be predicted from the reported effects of extracellular volume expansion on proximal tubular sodium reabsorption in both rats and dogs.[17,18,19,14] However, since we measured net tubular sodium reabsorption without discriminating between proximal and distal tubular uptake the magnitude of the volume induced proximal tubular depression would be obscured by this technique of measurement.

At first glance these findings seem to contradict our original suggestion that the sodium retention of cardiac failure involves altered tubular function. However it must be emphasized that we measured net tubular sodium reabsorption which represents the difference between active transcellular Na^+ transport and passive back-diffusion of sodium into the nephron lumen. A technique which we considered for indirectly evaluating the relative contribution of these two simultaneous processes in man was to determine the moles of sodium reabsorbed per mole of oxygen consumed, the results being expressed as a Na^+/O_2 ratio. Studies of the relationship between tubular reabsorption of sodium and renal oxygen consumption in animals indicate that approximately 30 equivalents of sodium are actively reabsorbed per mole of oxygen consumed.[27,28] Furthermore using pharmacologic blockade of the distal renal tubule of dogs Kjekshus, Aukland, and Kiil[28] concluded that the Na^+/O_2 ratios for proximal and distal tubular segments were similar. However the Na^+/O_2 ratio was observed to fall when mannitol diuresis was superimposed on distal tubular blockade, a finding which was best explained by enhanced passive back diffusion of sodium.[27] Our findings of a direct correlation between the Na^+/O_2 ratio and the glomerular filtration rate and an inverse

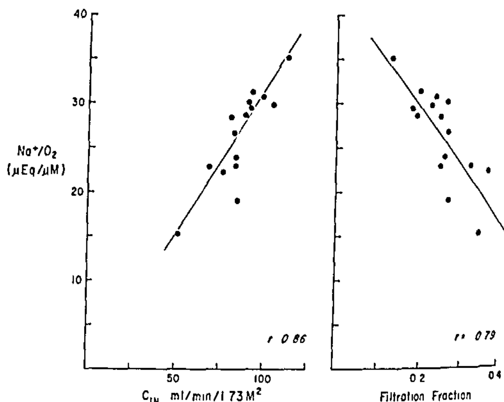


Fig. 11. Correlation plot of net sodium reabsorption per mole of oxygen consumed (Na^+/O_2) and glomerular filtration rate (C_{IN}) or filtration fraction. Constructed similar to Fig. 1.

studied. These data are shown in Fig. 11 where they are compared either to the glomerular filtration rate or to the filtration fraction. As can be seen, a direct correlation was present between GFR and Na^+/O_2 while an inverse relationship exists between filtration fraction and Na^+/O_2.

Discussion

Evidence regarding increased tubular sodium reabsorption as the intrinsic renal defect in both experimental and clinical heart failure has been recently summarized by Genest and colleagues.[9] Salient points of this review include (1) the impaired excretion of a hypertonic saline load in dogs with experimental heart failure when compared to the response in normal controls, (2) the finding of glomerular filtration rates that are within normal limits in patients with frank congestive heart failure and the observation that filtration rate decreased in some patients during decongestive treatment without impairing the response to diuretic drugs, (3) evidence of increased endogenous mineralocorticoid activity in patients with heart failure, and (4) absence of overt sodium retention in patients with renal artery stenosis despite marked reductions in both glomerular filtration rate and renal blood flow. However, a unified hypothesis regarding the mechanism responsible for this abnormal tubular retention has eluded investigators. Evidence favoring an increased tubular sodium reabsorption occurring in both the proximal[30,31] and distal tubule[3] further complicates definition of a pathophysiologic scheme consonant with divergent views. We have examined the relationship between systemic and renal hemodynamics present in a group of patients with valvular heart disease as they influence tubular reabsorption of sodium.

The preservation of a normal or near normal glomerular filtration rate in the face of a declining renal blood flow has been the basis for many explanations of the abnormal sodium retention of heart failure. However, extrapolating from the observations reported by Friedler and co-workers[33] that pharmacologically induced renal vasodilatation leads to a sodium diuresis in animals with experimental edema, Earley and Daugharty[34] suggest that "increased renal vascular resistance could result in

tation encountered in chronic anemia Evidence supporting intact glomerulo proximal tubular balance is presented along with a comparison of oxygen consumption per mole of sodium reabsorbed These data are compatible with either redistribution of intrarenal blood flow or with alteration of renal tubular sodium reabsorption downstream from the proximal portion of the nephron as the pathophysiologic explanation of the abnormal sodium retention of heart failure

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relationship to the filtration fraction suggest at least two interpretations The most obvious one is that with chronic heart failure a smaller percentage of renal energy derived from oxidative metabolism is involved in active tubular sodium reabsorption thus disturbing the expected close correlation between VO and active sodium transport [37] However, these findings are also compatible with an increased passive back diffusion of sodium into the tubular lumen since a reduced flow rate per nephron would provide more time for equilibration Mechanistic increased back diffusion could occur either along intracellular channels which have been demonstrated between the proximal tubular cells of dogs and rats [36,38] or by a preferential redistribution of intrarenal blood flow to juxtamedullary nephrons The latter possess longer descending loops of Henle which provide a greater surface area for passive re entry of sodium as well as the more favorable gradient which exists in the medullary area [1]

Support for both of these speculated mechanisms is available from animal studies Martino and Earley [39] using the intact dog kidney, presented evidence supporting the concept of proximal tubular sodium reabsorption being regulated by physical factors Alternatively Barger [1] has reported that blood flow to the outer cortex of the kidney is reduced following the induction of experimental heart failure in dogs Combined with previous observations that dogs undergoing a saline diuresis preferentially redistribute blood flow to the renal cortical region Barger concludes that the nephron population of the kidney has a spectrum of sodium retaining characteristics and the magnitude of sodium excretion is dependent upon the relative distribution of blood flow to these various nephrons Since cortical nephrons are less effective sodium retainers than deeper nephrons, the redistribution of intrarenal blood flow away from superficial nephrons impairs the excretion of excess sodium Our data do not allow a choice between these alternatives

Finally, the inverse correlation between cardiac output and renal O_2 extraction evident in Fig 8 suggests an adaptation similar to that reported with anemia Using dogs made chronically anemic by bleeding Aperia Liebow, and Roberts[40] have shown that the renal adaptation to the hypoxia of anemia is not through increased renal blood flow by vasodilatation but rather occurs from the widening of the arteriovenous oxygen difference due to an enhanced tissue Po gradient It is of interest that associated with the reduced filtration fraction which they observed (a result of a disproportionate decrease in glomerular filtration rate), the fractional tubular reabsorption of sodium increased These investigators concluded that the anemic animal retains normal renal function by reducing the filtered load of sodium and by more efficient O extraction both factors diminishing the work requirement of the organ It is possible that a similar renal adaptive mechanism may operate in chronic heart failure However instead of this mechanism representing a primary adaptation, this process in CHF could be initiated by increased cellular O_2 consumption resulting from increased tubular sodium reabsorption in an attempt to increase the vascular volume and thus improve cardiac filling pressure and raise cardiac output The lowered intracellular Po_2 would raise the gradient between cell and capillary and increase the oxygen diffusion rate culminating in increased renal oxygen extraction as measured by A V difference Thus despite the pathologic character of the increased sodium reabsorption in heart failure oxidative metabolism would not be rate limiting and thus would provide protection in conditions where sodium retention is critical to survival of the organism

Summary

The correlations between systemic hemodynamic parameters—i e , cardiac index mean left atrial pressure total blood volume and renal blood flow corrected for PAH extraction ratio are reported for 1 patients with compensated congestive heart failure In addition simultaneous measurements of net tubular sodium reabsorption and renal oxygen consumption were compared to both systemic and renal hemodynamic measurements The significant inverse correlation between cardiac index or renal blood flow and renal arteriovenous oxygen difference resembles the renal adap

Experimental and laboratory reports

Comparison of the effects of two anesthetic agents on the production of hypoxic pulmonary hypertension in dogs

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Hypoxia has been used to induce transient pulmonary hypertension in man[1,2] and in experimental animals.[3-5] Studies in dogs have been rendered difficult because a pulmonary arterial pressor response to the inhalation of low concentrations of oxygen does not occur in some dogs. This variability has led to the designation of two groups of dogs identified as "reactors" and "nonreactors."[5] This difference in reactivity has been variably attributed to the sensitivity of individual dogs to the depth of anesthesia, to an influence of the anesthetic agents on the vasomotor centers[10] and to a poorly understood time lag between the onset of anesthesia and the exposure to the low oxygen concentration.[5] The latter study suggested that all dogs became reactors if approximately eight hours elapsed between the onset of anesthesia and the hypoxic stimulus.

In the course of studies conducted in animals alternately breathing room air and gas with an inspired oxygen concentration of 8 per cent, it became apparent that our studies also were doomed to uncertainty because of the existence of "reactors" and "nonreactors." This initial group of dogs had been anesthetized with sodium pentobarbital, as has been the case in prior studies with animals.[4,5] The increasing evidence that pentobarbital anesthesia profoundly modifies many cardiovascular functions[11,12] led us to hypothesize that the anesthetic was the source of the variability. We then conducted a comparative experimental trial of the effects of hypoxia using dogs anesthetized either with sodium pentobarbital or with a mixture of droperidol and fentanyl.

The pharmacologic actions of droperidol† include central nervous system depression manifested by marked reduction in spontaneous motor activity, a loss of responsiveness to normal environmental sounds, minimal respiratory depression, a tendency to sleep, with little effect on the cardiovascular system at a dose which produces a sedative or depressant effect.[13]

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Table I Data obtained before and during hypoxia in dogs anesthetized with pentobarbital (Group A) or a droperidol fentanyl mixture (Group B)

	Po_2 (mm Hg)	pH	Pco_2 (mm Hg)	Cardiac output (L/min)	Heart rate (beats/min)	Mean pulmonary artery pressure (mm Hg)	Mean wedge pressure (mm Hg)
Room air							
Group A							
No	19	22	21	20	22	22	18
Mean	91	7.34	[illegible]	4.17	106	15.3	4.4
S.E.	3.1	0.01	1.71	0.36	6.66	[illegible]	0.85
Group B							
No	17	18	18	18	18	18	17
Mean	[illegible]	7.31	40.5	[illegible]	93	[illegible]	[illegible]
S.E.	[illegible]	0.01	0.01	1.08	5.84	0.55	0.46
p	N.S.	<0.05	<0.01	<0.01	<0.001	<0.001	N.S.
8 per cent oxygen							
Group A							
No	8	8	8	20	22	22	16
Mean	34.5	7.49	23.6	4.31	204	17.7	[illegible]
S.E.	2.2	[illegible]	1.89	0.36	5.87	1.44	[illegible]
Group B							
No	17	18	18	18	18	18	18
Mean	36.5	7.44	27.8	3.0	134	[illegible]	3.4
S.E.	1.4	0.01	0.99	0.17	10.5	77	[illegible]
p	N.S.	<0.10	<0.05	<0.01	<0.001	[illegible]	N.S.

N.S. = not significant

tanyl group while the dogs were breathing room air probably reflecting slight differences in respiratory depression The mean pulmonary arterial pressures while breathing room air differed significantly with an average value of 15.3 ± 1.3 S.E. mm Hg in those dogs anesthetized with pentobarbital and 9.7 ± 0.5 mm Hg in the dogs anesthetized with droperidol fentanyl Pulmonary hypertension developed during the first minute of breathing 8 per cent oxygen reached a stable level by the fifth minute and returned to control levels within two minutes after the dogs again breathed room air

It is well known that acidosis and hypercapnia induce pulmonary hypertension From this one might have expected that the droperidol fentanyl group would have had higher initial pulmonary artery pressures than the pentobarbital group Left atrial pressure assessed as the pulmonary arterial wedge pressure did not differ between the two groups It seems most likely that the difference in mean pulmonary artery pressure between the two groups reflects the higher cardiac output found in the pentobarbital group This was tested by calculating the pulmonary vascular resistance levels These were not different in the two groups with average values of 291 dynes sec cm^{-5} and 280 dynes sec cm^{-5} respectively

Only 13 of the 22 dogs which received pentobarbital anesthesia developed pulmonary hypertension in response to the 8 per cent oxygen–inhaled gas mixture Conversely all 18 dogs which received droperidol fentanyl anesthesia developed a pulmonary pressor response to hypoxia This qualitative difference in frequency is highly significant (p = 0.0005) as calculated by the exact probability method of Fisher[17] These data indicate that a change in the anesthetic agent abolished the apparent reactor nonreactor dichotomy among dogs exposed to a hypoxic inhaled gas mixture

The pharmacologic actions of fentanyl* resemble those of morphine. The duration of action is brief, with a half time of 15 to 20 minutes. A mild hypotensive effect and sinus bradycardia usually occur, the latter is immediately antagonized by atropine. The vagi play a major role in the production of this bradycardia because this action is significantly reduced in bilaterally vagotomized dogs. The mild hypotensive response is not due to a cholinergic or histamine-like effect since it is not blocked by vagotomy, atropine, or antihistamines.[14,15]

Both droperidol and fentanyl have their own effects without well-defined antagonistic or potentiating interactions, except that droperidol enhances the analgesic activity of fentanyl. The combination produces potent analgesia and sedation.

Materials and methods

Forty mongrel dogs of both sexes, divided into two consecutive groups, were studied utilizing the same protocol but with different anesthetic agents. The initial 22 animals (weight range 13.4 to 22 kilograms, mean 17.7 kilograms) were anesthetized with sodium pentobarbital† administered intravenously in a dose of 30 mg. per kilogram. The subsequent 18 dogs (weight range 12.3 to 23.5 kilograms, mean, 16.2 kilograms) received a mixture of 20 mg. of droperidol and 0.4 mg. per cubic centimeter of fentanyl‡ in a dose of 0.3 ml. per kilogram. Supplemental doses of 30 mg. of pentobarbital or 0.5 to 1.0 c.c. of droperidol-fentanyl were given as necessary to ensure continued anesthesia. Each dog receiving droperidol-fentanyl also received 0.4 mg. of atropine sulfate subcutaneously at the time of droperidol-fentanyl administration. A cuffed endotracheal tube ensured a leak-free system; the dogs breathed spontaneously.

The thoracic aorta, the pulmonary arterial wedge position, and the main pulmonary artery were catheterized from the femoral vessels under fluoroscopic control. Pulmonary wedge position was determined by catheter tip location and by pulse pressure contour. Pressures were recorded at a paper speed of 10 mm. per second using Statham P23Db strain gauges and the carrier amplifiers of an oscillographic recorder. Electrocardiographic Lead II was recorded simultaneously. Mean pressures were obtained by electronic damping.

Cardiac output was measured by the indicator dilution technique. Indocyanine green was injected as a sudden bolus of 2.5 mg. into the pulmonary artery. Aortic blood was withdrawn through a densitometer with a constant rate withdrawal syringe. Each indicator dilution curve was replotted on semilogarithmic paper; cardiac outputs were calculated using the Hamilton method.[16]

The same protocol was used for each dog. Initial measurements of pulmonary arterial, pulmonary arterial wedge, and aortic pressures were made while the dogs breathed room air approximately 15 to 20 minutes after the initiation of anesthesia. Then approximately ten minutes were permitted to elapse to ensure stability of these values before arterial P_{O_2}, P_{CO_2}, pH, and cardiac output were measured. The endotracheal tube was then connected to a reservoir containing a gas mixture of 8 per cent oxygen and 92 per cent nitrogen, using a one-way valve which did not permit rebreathing.

Pulmonary arterial, pulmonary wedge, and aortic pressures were measured at one minute intervals after the onset of hypoxi[illegible]. Measurements of heart rate, cardiac output, and blood gases were repeated ten minutes after the introduction of the hypoxic stimulus. It was observed that the intrinsi[illegible] variation of the mean pulmonary arter[illegible] pressures was less than ±1 mm. Hg while the animals were spontaneously breathin[illegible] room air; an increase of more than 1.5 mm. Hg was considered a positive response t[illegible] hypoxia.

Results

The results of specific measurement[illegible] made are summarized in Table I. As i[illegible] indicated, the two groups of dogs had com[illegible]parable control arterial P_{O_2} values. Cardia[illegible] outputs and heart rates were significantl[illegible] higher in the group of animals anesthetize[illegible] with pentobarbital. The arterial pH wa[illegible] slightly but significantly lower and th[illegible] P_{CO_2} values higher in the droperidol-fen[illegible]

*Sublimaze, McNeil Laboratories, Inc., Fort Washington, Pa.
†Diabutal, Diamond Laboratories, Inc., Des Moines, Iowa.
‡Innovar-Vet, McNeil Laboratories, Inc., Fort Washington, Pa.

The average calculated pulmonary arteriolar resistance increased from 290 to 353 dynes sec cm^{-5} without significant change in the pulmonary arterial wedge pressure This analgesic neuroleptic combination provides satisfactory anesthesia for studies of hypoxic pulmonary hypertension in dogs

We are greatly indebted to Mr Michael Hacklin for his valuable technical assistance and to Mrs. Linda Campbell and Mrs Shirley William for their able secretarial assistance

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The average mean pulmonary arterial pressure rose in the pentobarbital group but a higher increase of 3.5 mm. Hg in the average value was found in the droperidol-fentanyl group. The "reactor" or "nonreactor" status of dogs in the pentobarbital group was not related to pH or to P_{CO_2}. For example, five dogs in the pentobarbital group had arterial pH values less than 7.30. Of these five, two developed a pulmonary pressor response with hypoxia and three failed to react. Six dogs in the droperidol-fentanyl group had control arterial pH values of less than 7.30; each developed a pressor response with hypoxia. Moreover, the minimal role of the arterial pH in modifying the pulmonary pressor response is indicated by the insignificant difference in arterial pH values obtained in the two groups during hypoxia. The higher heart rate and cardiac output encountered in the control state persisted after hypoxia in the pentobarbital group. That the appearance of pulmonary hypertension in the droperidol-fentanyl group reflected active pulmonary vasoconstriction is attested by the lack of change in the wedge pressure and by an increase of 73 dynes sec. cm^{-5} in the average calculated pulmonary arteriolar resistance.

The observation that the central pulmonary artery pressure was higher in dogs which received pentobarbital than in those which received droperidol-fentanyl led to chronic studies in one dog after leaving a catheter in the main pulmonary artery. The mean pulmonary arterial pressure varied from 11.5 to 12 mm. Hg during anesthesia with droperidol-fentanyl. On the following day the pressure was also 11.5 to 12 mm. Hg while the dog was awake. Subsequently, administration of sodium pentobarbital (30 mg. per kilogram) was associated with an increase in pulmonary arterial mean pressure to 13 and 14.5 mm. Hg at five and ten minutes, respectively.

The variability in the pulmonary vascular reactivity of the pentobarbital group was further evidenced by one dog which underwent consecutive studies three days apart. A pulmonary pressor response occurred to hypoxia during the first study; no change in mean pulmonary arterial pressure occurred with exposure to the same stimulus during the second study.

Discussion

The response of the pulmonary vascular bed to hypoxia has varied widely in previous studies.[7] The only exceptions are the report of Borst and associates,[5] in which hypoxic pulmonary hypertension uniformly occurred in dogs after six to eight hours of anesthesia, and the report of Thilenius and associates,[8] in intact, unanesthetized dogs. The variability reported in other studies[5-10] seemed unlikely to reflect intrinsic differences among dogs. The influence of the anesthetic agent on the development of hypoxic pulmonary hypertension was the subject of the present study. As has been previously found, dogs studied under barbiturate anesthesia reacted variably to hypoxia. Conversely, dogs studied under droperidol-fentanyl anesthesia uniformly developed hypoxic pulmonary hypertension. This group of dogs received small amounts of atropine to counteract the sinus bradycardia produced by these agents. The effect of atropine on the pulmonary arterial pressure, regardless of the change in cardiac output, is known to produce either an increase, a decrease, or no change in pressure.[15] One may postulate, however, that atropine could enhance the development of hypoxic pulmonary vasoconstriction by blocking the inhibitory effect of vagal stimulation on the release of histamine.[16] It has been shown that atropine does not modify the hypoxic pressor response.[7]

A combination of droperidol and fentanyl provides satisfactory anesthesia and permits the demonstration of a pulmonary vasoconstrictor response in the dogs studied. A mixture of droperidol and fentanyl may prove to be superior to pentobarbital anesthesia for physiologic experimentation in the study of hypoxic pulmonary hypertension.

Summary

Inhalation of 8 per cent oxygen produced pulmonary hypertension in only 13 of 22 dogs anesthetized with pentobarbital. Conversely, each of the dogs anesthetized with a mixture of droperidol and fentanyl developed hypoxic pulmonary hypertension ($p = 0.0055$) with an increase in the average mean pulmonary artery pressure from 9.7 ± 0.55 (S.E.) to 13.2 ± 0.77 mm. Hg

The average calculated pulmonary arteriolar resistance increased from 280 to 353 dynes sec cm $^{-5}$ without significant change in the pulmonary arterial wedge pressure. This analgesic neuroleptic combination provides satisfactory anesthesia for studies of hypoxic pulmonary hypertension in dogs.

We are greatly indebted to Mr. Michael Hacklin for his valuable technical assistance and to Mrs. Linda Campbell and Mrs. Shirley Williams for their able secretarial assistance.

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Summary

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Table I. Hemodynamic results of coronary embolization and effects of dopamine (mean ± S.E.M.)

Parameters	Control (N = 1)	Postembolic (N = 1)	Dopamine 90 min (N = 1)	Dopamine 60 min (N = 1?)	No drugs (N = 10)
Heart rate (beats/min.)	159 ± 7 ?	15? ± 5 4	151 ± 6 9	151 ±	1?? ± ? 8
Cardiac output (L/min.)	4 19 ± 0 40	03 ± 0 17	6 ± 0 21	3? ± 0 1?	1 5 ± 0 14
LV stroke volume (ml./beat)	6 1 ± ?	13 3 ± 1 0	1 4 ± 1 3	15 ± 1 ?†	1 ± 1 **
LV systolic pressure (mm. Hg)	1?3 ± 10	140 ± 11 0	15? ± 11 6†	148 ± 11 0	1 4 ± 8 8
LV end-diastolic pressure (mm. Hg)	7 3 ± 1 ?	1? 8 ± 4	14 ± 6†	14 8 ± ? ?	19 9 ± 3 3
Mean aortic pressure (mm. Hg)	14 ± 8 ?	128 ± 9 6	134 ± 9 8	130 ± 10 1	11 ± 8 0
Systemic vascular resistance (dynes sec cm.⁻⁵)	? 950 ± 308	5 256 ± 381	4 3?0 ± 470†	4 ? 0 ± 408	4 900 ± 41?†
LV minute work (Kg. M./min.)	9 3 ± 1 3	3 5 ± 0 5	5 1 ± 0	4 4 ± 0 6	? 8 ± 0 4
LV stroke work (Gm. M./min.)	58 0 ± 7 4	?3 ± 3 3	33 8 ± 4 5	?9 8 ± 4 3	18 4 ± 3 0
LV peak dP/dt (mm. Hg/sec.)	3 060 ± 33?	? 17 ± ?60*	3 5?? ± 419	3 3?8 ± 338	1 83? ± 19?
Pressure-time index (mm. Hg beat/min. 10⁻³)	2?? ± 18	?1 ± 18	?28 ± 19	??1 ± 16	191 ± 13

N = N mb of d gs.
*p < 0.01
†p < 0.05
p al r fe t th s fi ce f p ired d fferences.

with the electrocardiogram using a multichannel photographic recorder (Electronics for Medicine). The first derivative of the left ventricular pressure (LV dP/dt) was obtained by electronic differentiation. Cardiac output was measured by the indicator dilution technique, indocyanine green (2.5 mg.) being injected into the main pulmonary artery and sampled continuously from the descending aorta through a Waters XP 302 densitometer using a Gilford constant flow infusion withdrawal pump and the curves calibrated by the Sparling method.[8] Systemic and pulmonary vascular resistances and left ventricular stroke and minute work were calculated by standard formulas. A pressure time index was obtained as the product of the left ventricular systolic pressure and heart rate.[9] Selective embolization of the left coronary artery was performed using a modification of the technique of Fluch and associates[10] as described previously.[11,24] Postembolic control measurements were obtained 90 to 120 minutes after the second mercury injection at which time a stable hemodynamic state and heart rhythm were present.

Dopamine* was infused at the rate of 5 μ per kilogram per minute into a peripheral vein and the hemodynamic responses determined at 20 and 60 minutes. Where dopamine caused persistent ventricular dysrhythmias the infusion was reduced to 2.2 μg per kilogram per minute. Final hemodynamic measurements were made 30 minutes after stopping the dopamine infusion.

Results

The hemodynamic changes produced by coronary embolization, dopamine infusion, and final control values are given in Table I.

*Obt ned th gh th court sy of A n r Stone Labo tori s, Mou t P pect Ill.

The effects of dopamine on depressed myocardial function following coronary embolization in the closed-chest dog

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Sympathomimetic amines increase myocardial contractility and are used to treat cardiogenic shock and severe cardiac failure.[1,2] While norepinephrine, epinephrine, and isoproterenol have been the most frequently administered drugs for their positive inotropic effect, excess alpha or beta adrenergic receptor stimulation has frequently limited their ultimate effectiveness.[3,4] Dopamine (3,4-dihydroxyphenylethylamine), an immediate metabolic precursor of norepinephrine, has been suggested as an alternative drug and preliminary studies have been published documenting its effect in the management of cardiogenic shock and severe cardiac failure.[5-7]

This study reports the hemodynamic effects of dopamine on depressed myocardial function produced in the closed-chest dog by mercury embolization of the left coronary arterial system.

Method

Twelve mongrel dogs whose weights varied from 25 to 34 kilograms were anesthetized with sodium pentobarbital (25 mg per kilogram). Additional muscle relaxation was induced with intermittent 20 mg doses of succinylcholine as needed. Respiration was maintained by room air delivered through a cuffed endotracheal tube from a positive pressure pump (Harvard). Arterial Po_2, Pco_2, and pH were monitored frequently throughout the experiment and adjustments made to the respiratory cycle as needed. Metabolic acidosis was corrected by intermittent intravenous injections of 20 to 40 mEq of sodium bicarbonate as required. Ducor catheters (7 or 8 F.r.) were placed in the ascending aorta and main pulmonary artery from the left femoral artery and vein, respectively, under fluoroscopic control. High fidelity left ventricular pressure recordings were obtained by transthoracic insertion of a 4 inch semirigid Teflon cannula (Becton Dickinson & Co.) attached directly to the pressure transducer. All pressures were measured with reference to the midchest position using Statham P23Db transducers and recorded simultaneously

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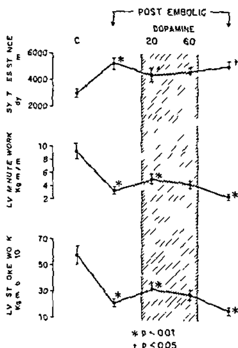


Fig 1C Hemodynamic result (LV stroke work LV minute work systemic resistance) of coronary embolization and the effects of dopamine infusion at 20 minutes and 60 minutes after the postembolization control determinations

Discussion

Despite the vigorous administration of a variety of sympathomimetic amines the mortality rate from cardiogenic shock remains unacceptably high[4] These pharmacologic agents act through varying degrees of beta and alpha adrenergic stimulation[12] Excessive alpha adrenergic stimulation may impair peripheral and visceral perfusion[13] and increase myocardial afterload thereby reducing cardiac output and increasing myocardial oxygen consumption[14,15] Excessive beta adrenergic stimulation despite its significant inotropic effect may produce a fall in systemic blood pressure and hence in coronary artery perfusion[16] The associated sinus tachycardia further increases myocardial oxygen consumption and ventricular rhythm disturbances may emerge[4,17] Of even greater concern are reports of subendocardial necrosis following large doses of sympathomimetic amines[18] and more recently extension of ischemic zones surrounding the infarct as defined by electrocardiographic surface mapping techniques have been noted[19]

Dopamine (3 4-dihydroxyphenylethylamine), a naturally occurring catecholamine and immediate precursor of norepinephrine produces both alpha and beta adrenergic stimulation[20,21] Hemodynamic studies in normotensive human subjects and animals have demonstrated increased cardiac output and myocardial contractility mediated through beta adrenergic stimulation The peripheral vascular response has been variable depending on the species of animal and the dose administered[7] In the normal human subject increased myocardial contractility is associated with a fall in systemic vascular resistance and minimal change in heart rate and arterial blood pressure[2*]

Dopamine induces vasodilation of the renal[3,4] and mesenteric vascular beds[23] Improvement in renal plasma flow glomerular filtration and sodium clearance have been documented This property is not related to beta adrenergic stimulation and appears unique to dopamine In contrast commonly used agonist agents may reduce renal blood flow through renal artery constriction by reduction in perfusing pressure or shunting blood from the kidneys to the extremities[8]

Studies using dopamine in the intact animal preparation with depressed myocardial function have been few Wintroub and associates[8] induced myocardial depression by ligation of the anterior descending coronary artery in the open chest dog Significant increases in cardiac output LV dP/dt associated with fall in systemic vascular resistance occurred heart rate and mean arterial blood pressure remained unchanged Carvalho and associates[27] utilizing either circumflex coronary artery ligation or microsphere embolization in an open chest preparation noted similar results Systemic vascular resistance however remained unchanged and both the heart rate and mean blood pressure rose Significant increase in coronary blood flow occurred In both these studies myocardial irritability during dopamine infusion was not a significant problem

In the present study mercury embolization of the left coronary artery of the dog

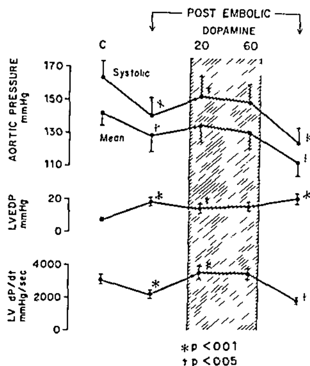


Fig. 1A. Hemodynamic results (LV dP/dt, LVEDP, and aortic pressure) of coronary embolization and the effects of dopamine infusion at 20 minutes and 60 minutes after the postembolization control determinations.

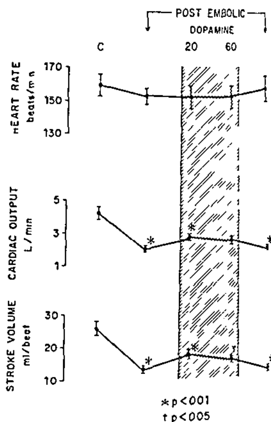


Fig. 1B. Hemodynamic results (stroke volume, cardiac output, and heart rate) of coronary embolization and the effects of dopamine infusion at 20 minutes and 60 minutes after the postembolization control determinations.

and shown graphically in Fig. 1. All results were analyzed statistically and represent the mean ± S.E.M. of the 12 experiments.

Selective embolization of the left coronary arterial system. Ninety to 120 minutes following selective embolization of the left coronary artery the cardiac output fell by 52 per cent, stroke volume by 49 per cent, left ventricular peak dP/dt by 29 per cent, left ventricular systolic pressure by 14 per cent, left ventricular stroke work by 60 per cent, and pressure time index by 18 per cent. In contrast, the systemic vascular resistance increased 77 per cent and left ventricular end diastolic pressure from a control value of 7 to a value of 18 mm. Hg.

Dopamine infusion. Twenty minutes after starting the dopamine infusion significant increases in cardiac output (30 per cent), stroke volume (31 per cent), stroke work (46 per cent), left ventricular dP/dt (64 per cent), and left ventricular systolic pressure (8 per cent) were recorded. The systemic vascular resistance decreased by 18 per cent and the left ventricular end diastolic pressure decreased from 18 to 14 mm. Hg. Heart rate and mean aortic pressure did not change significantly.

After 60 minutes of continuous dopamine infusion a significant decrease in stroke volume occurred (14 per cent) with all other parameters remaining unchanged.

Cessation of dopamine. Thirty minutes after stopping the dopamine infusion marked hemodynamic deterioration occurred with significant reduction in cardiac output (21 per cent), stroke volume (2? per cent), stroke work (38 per cent), peak LV dP/dt (45 per cent), and pressure time index (13 per cent). The systemic vascular resistance increased (9 per cent) and the left ventricular end-diastolic pressure rose from 15 to 20 mm. Hg; the heart rate remained unchanged.

Persistent ventricular dysrhythmias occurred in 6 dogs and in 4 recurrent ventricular tachycardia necessitated reducing the dopamine infusion from 5 to 2.2 μg per kilogram per minute. Ventricular fibrillation did not occur during the infusion of the drug.

persistent ventricular tachycardia It is concluded that dopamine will improve depressed myocardial function following acute coronary arterial embolization at least temporarily but that the incidence of serious ventricular dysrhythmias may well limit its use

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provided a reproducible model of depressed myocardial function in the intact animal resembling that seen in patients with extensive myocardial infarction[28] This *hemodynamic response is characterized by* a fall in cardiac output and work mean blood pressure, and left ventricular dP/dt, and by a rise in left ventricular end diastolic pressure and systemic vascular resistance[11]

Dopamine significantly improved myocardial function as shown by an increase in cardiac output, stroke volume left ventricular dP/dt, and left ventricular stroke work and by a fall in left ventricular end diastolic pressure A positive inotropic response to dopamine was indicated by the increase in left ventricular dP/dt associated with an unchanged heart rate, mean blood pressure and a fall in systemic vascular resistance and left ventricular end diastolic pressure

Although coronary blood flow was not determined in the present study, dopamine is a potent stimulator of coronary blood flow The induced coronary vasodilation is however secondary to increased myocardial oxygen demands[29]

The evaluation of dopamine in the treatment of cardiac failure[2,6] and cardiogenic shock[5,7] in patients has been limited Significant diuretic response characterized by increased glomerular filtration rate and sodium excretion was noted in patients with congestive cardiac failure Marked hemodynamic improvement occurred in 3 of 7 patients with cardiogenic shock following acute myocardial infarction or cardiac surgery These patients had been refractory to norepinephrine, epinephrine and mannitol[30] In shock due to varying etiologies *comparative* hemodynamic studies of dopamine and the other commonly used sympathomimetic amines suggested dopamine to be more effective than isoproterenol in the presence of normal or reduced peripheral vascular resistance[31] and superior to norepinephrine in patients requiring little elevation in mean arterial pressure[3] Unlike norepinephrine and isoproterenol which produced transmyocardial lactate Winslow and associates[32] observed increased myocardial lactate extraction in shocked patients treated with dopamine

Of particular concern in this study was the high incidence of ventricular dysrhythmias unassociated with significant chronotropic response Rhythm disturbances have not been documented as a significant problem even when dopamine was used in higher doses than in the current study While the increased myocardial irritability might be a reflection of the model of depressed myocardial function used significant dysrhythmias were not observed in a similar animal preparation infused with low-dose isoproterenol and aminophylline[34]

This study demonstrates that dopamine significantly improves myocardial function when acutely depressed The pharmacologic properties of the amine appear advantageous, for not only is there improvement in cardiac function but also renal function The emergence of ventricular dysrhythmias however is of concern and requires further evaluation

Summary

Severe myocardial depression was induced in 12 anesthetized closed chest dogs by mercury embolization of the left coronary artery and the effects of dopamine infusion (5 μg per kilogram per minute) studied Coronary embolization produced decreases in cardiac output (CO) of 52 per cent stroke volume (SV) of 49 per cent left ventricular peak dP/dt (LVdP/dt) of 29 per cent stroke work (SW) of 60 per cent, LV systolic pressure (LVSP) of 14 per cent and an increase in systemic vascular resistance (SVR) of 77 per cent. LV end diastolic pressure (LVEDP) increased from 7 to 18 mm Hg After 30 minutes of dopamine CO increased 30 per cent, SV 31 per cent SW 46 per cent LVdP/dt 64 per cent and LVSP 8 per cent, SVR decreased 18 per cent and LVEDP was 14 mm Hg (all changes $p < 0.05$) Heart rate and mean aortic pressure did not change After 60 minutes of dopamine slight deterioration occurred but most parameters were still significantly improved Thirty minutes after stopping dopamine marked circulatory deterioration recurred Persistent ventricular dysrhythmias occurred in 6 dogs in 4 of whom dopamine dosage had to be decreased to 2.5 μg per kilogram per minute because of

Effect of caffeine on the ventricular fibrillation threshold in normal dogs and dogs with acute myocardial infarction

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Recently our laboratory as well as others has been interested in studying the various stress effects of caffeine such as the elevation of plasma adrenocortical steroid concentrations blood free fatty acid levels and adrenergic effects [1-8] In addition caffeine may increase the concentration of cyclic adenosine monophosphate (AMP) by competitive inhibition of phosphodiesterase and may decrease the binding of Ca^{++} by the cell membrane [9,10] Because some of these pharmacologic effects are known to induce ventricular fibrillation [11,12] it would be of interest to study the effect of caffeine on the ventricular fibrillation threshold (VFT)

The aim of the present work was to study the effect of caffeine on the VFT in normal dogs and in dogs with experimentally induced myocardial infarction during the acute stage of the occlusion In order to evaluate the relation of the changes in VFT after the administration of caffeine to the adrenergic effects experiments were also performed after pretreatment with propranolol and with practolol

Methods and materials

Mongrel dogs weighing 25 to 30 pounds were anesthetized intravenously with sodium pentobarbital 25 mg per kilogram of body weight Respiration with room air was maintained by means of a Harvard ventilatory pump through an endotracheal tube Tidal volume and respiratory rate were set according to the weight of the animal utilizing the ventilatory graph prepared by Kleinman and Radford Arterial

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*****R sear h Associat D is of C d l gy Phil d lphia Ge al H pital.

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*Table I Effect of sodium benzoate on the ventricular fibrillation threshold in intact normal dogs**

Dog	Minutes after intravenous injection					
	0	15	30	45	60	90
1	0 50†	0 50	0 45	0 50	0 55	0 50
2	0 45	0 45	0 50	0 45	0 45	0 45
3	0 45	0 40	0 40	0 40	0 40	0 40
4	0 35	0 35	0 40	0 35	0 40	0 35
5	0 70	0 70	0 70	0 70	0 70	0 70
6	0 50	0 50	0 45	0 50	0 50	0 50
7	0 70	0 70	0 70	0 75	0 75	0 75
8	0 60	0 60	0 60	0 60	0 45	0 45
9	0 30	0 30	0 30	0 20	0 20	0 25
10	0 45	0 40	0 45	0 45	0 55	0 55

Time after drug admin (min)	No of dogs	Mean VFT (watt sec)	Mean difference from 0 time value (watt sec)	Variance	S E M	t	P
0	10	0 50					
15	10	0 49	0 01	0 0444	0 067	0 149	N S‡
30	10	0 495	0 005	0 00136	0 011	0 454	N S
45	10	0 49	0 01	0 00155	0 012	0 833	N S
60	10	0 495	0 005	0 0058	0 024	0 [illegible]08	N S
90	10	0 49	0 01	0 0043	0 02[illegible]	0 50	N S

*Dosage 12.5 mg per kilogram of body weight
†VFT in watt seconds.
‡Differences [illegible] statistically significant [illegible] the 5 [illegible] level [illegible] of a paired comparison.

wall and were thus available for stimulation

Group A In the first group (Group A intact dogs) a method similar to that described by Lown Kleiger and Williams[13] was utilized Caffeine and control experiments were performed on normal dogs and on dogs with acute myocardial infarction The method is briefly as follows Two electrode paddles measuring $8\frac{1}{2}$ cm in diameter covered with conductive paste were applied with pressure externally on both sides of the shaved chest at the level of the apical thrust These paddles were held in a fixed position with rubber straps across the chest Electrical discharges were delivered utilizing the Lown Cardioverter Model 10530 I with a 16 microfarad capacitor through a 100 millihenry inductor A voltage-dividing network was connected in series with the electrodes in order to obtain accurate measurement of the discharge at the range of 0 to 10 wsec (watt seconds) at increments of 0 05 wsec The fibrillation threshold was determined by sweeping the Q T interval of the cardiac cycle with stimuli of increasing energy from subthreshold to threshold levels This was performed by progressively increasing the delay of the stimulus from the peak of the R wave by increments of 10 milliseconds using a 15 to 20 second interstimulus interval The criterion of the VFT was the minimal energy producing ventricular fibrillation for at least 10 seconds The presence of ventricular fibrillation was established by the ECG and the disappearance of pulsatile aortic pressure (Fig 1) Countershocks with energy ranging from 50 to 200 wsec were applied in order to convert ventricular fibrillation to normal sinus rhythm After an episode of ventricular

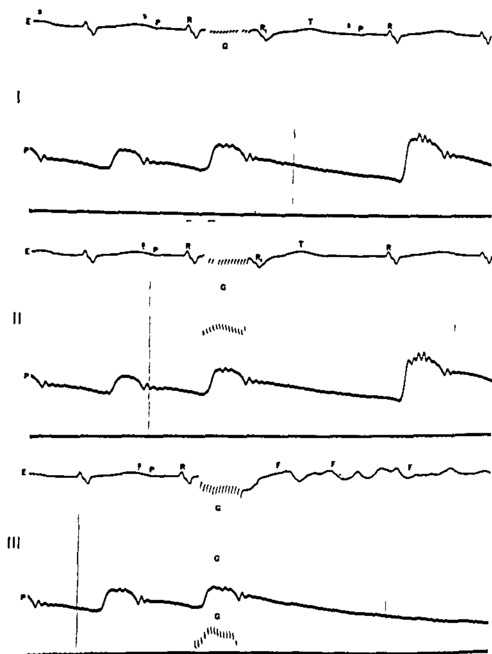


Fig. 1. Determination of the ventricular fibrillation threshold (VFT) by delivering a gated series of impulses (G) through previously implanted epicardial electrodes S pacemaker stimulus R ventricular complex F ventricular fibrillation Note the progressive increase of the amplitude of the gated impulse (G) from I to III

pH, Pco_2 and Po_2 were monitored by the use of a radiometer The values did not show significant deviation from the normal The temperature was recorded every 15 minutes by means of a rectal thermometer The electrocardiogram (ECG) was monitored through an oscilloscope and recorded each time the VFT was measured with a Sanborn Viso 100 recorder at a paper speed of 50 mm per second The blood pressure was measured by means of a catheter inserted in the descending aorta utilizing Statham 23Bd transducers and Electronics for Medicine amplifiers

Two groups of experiments were performed In the first group the ventricular fibrillation threshold (VFT) was determined in intact dogs by delivering electrical impulses through the chest wall In the second group the impulses were delivered directly to the heart through previously implanted epicardial electrodes These electrodes were attached to insulated wires which were exteriorized through the chest

*Table III Effect of sodium benzoate on the ventricular fibrillation threshold in normal dogs with bipolar implanted electrodes (third to seventh day after implantation)**

Dog	Minutes after intravenous injection						
	0	15	30	45	60	90	120
1	14†	16	14	16	16	16	15
2	16	15	13	16	15	15	13
3	18	17	18	18	19	19	16
4	16	18	18	16	15	18	—
5	12	11	11	13	13	11	12
6	10	9	10	10	9	10	10
7	9	11	10	10	10	11	9
8	17	19	20	18	19	19	18
9	12	11	11	11	12	12	10
10	12	12	12	13	9	12	14

Time after admin. of sodium benzoate (min.)	No. of dogs	Mean VFT (Ma.)	Mean difference from 0 time value (Ma.)	Variance	S.E.M.	t	P
0		13.6					
15	10	13.9	0.3	2.233	0.47	0.64	N.S.‡
30	10	13.7	0.1				N.S.
45	10	14.1	+0.5	0.7272	0.269	1.859	N.S.
60	10	13.7	0.1				N.S.
90	10	14.3	+0.7	1.555	0.394	1.776	N.S.
120	10	13.0	−0.3	2.4444	0.494	0.668	N.S.

*Dose: 12.5 mg. per kilogram of body weight.
†VFT in milliamperes.
‡Difference not statistically significant.

planted electrodes) electrical discharges were delivered directly to the myocardium by means of specifically constructed bipolar epicardial electrodes implanted on the right ventricle three to seven days prior to the experiment. These electrodes consist of two stainless steel wires 1 mm. in diameter embedded 10 mm. apart in a small acrylic plaque. They were connected to Teflon coated treated silver wires which were exteriorized through the chest wall. The heart rate was kept constant during each experiment by pacing the right atrium at a rate above the spontaneous rate of the animal by means of a similar pair of implanted electrodes. An American Electronics Laboratory stimulator was utilized for this purpose. The pacemaker impulse was double the pacing threshold in intensity and

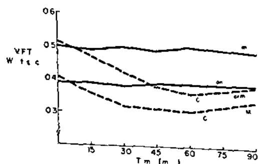


Fig. 2 The effect of caffeine on the VFT of normal dogs and dogs with acute myocardial infarction (impulses delivered through the chest wall). No change in the normal control. Following caffeine administration the VFT drops. The control values of dogs with acute myocardial infarction (A.M.I.) are lower than normal. Further decrease is observed after caffeine.

*Table II. Effect of caffeine sodium benzoate on ventricular fibrillation threshold in intact normal dogs**

Dog	Minutes after intravenous injection					
	0	15	30	45	60	90
1	0 65†	0 50	0 55	0 50	0 55	0 40
2	0 50	0 50	0 35	0 30	0 30	0 35
3	0 50	0 50	0 40	0 40	0 45	0 45
4	0 50	0 40	0 35	0 35	0 35	0 35
5	0 40	0 40	0 35	0 30	0 35	0 35
6	0 50	0 45	0 40	0 35	0 25	0 35
7	0 45	0 45	0 50	0 40	0 35	0 35
8	0 50	0 45	0 35	0 30	0 30	0 40
9	0 55	0 55	0 50	0 40	0 30	0 40
10	0 35	0 30	0 30	0 30	0 25	0 25
11	0 70	0 70	0 60	0 60	0 50	0 55

Time after admin of caffeine (min)	No of dogs	Mean VFT (watt sec)	Mean difference from 0 time value (watt sec)	Variance	S E M	t	P
0	11	0 509					
15	11	0 473	0 036	0 002546	0 0152	3 368	0 05
30	11	0 423	0 086	0 001307	0 0110	7 818	0 001
45	11	0 382	0 127	0 002682	0 0120	10 580	0 001
60	11	0 359	0 150	0 005500	0 0224	6 696	0 001
90	11	0 382	0 127	0 003182	0 0170	7 470	0 001

*Dosage 25 mg per kilogram of body weight
†VFT in watt seconds

fibrillation a period of at least 10 minutes was allowed before a new series of stimuli were applied

The ventricular fibrillation threshold (VFT) was determined in 11 normal dogs at 15 minute intervals before and for a period of 90 minutes after intravenous injection of 25 mg per kilogram of body weight caffeine sodium benzoate (corresponding to 12 5 mg per kilogram of body weight caffeine base) Control experiments of the same duration in which sodium benzoate (12 5 mg per kilogram of body weight) was injected, were performed in 11 other dogs

Similar studies were performed also in dogs during the acute phase of myocardial infarction produced by two stage ligation of the anterior descending artery [11] The experiments were performed on the fourth day after coronary ligation because in an earlier stage the presence of frequent premature ventricular contractions interferes with the proper determination of the VFT Caffeine experiments were performed in 11 dogs with acute infarction, whereas control experiments were performed in 6 such dogs

In addition similar experiments were performed on 9 normal animals treated by a combination of caffeine sodium benzoate (25 mg per kilogram of body weight) and propranolol (0 2 mg per kilogram of body weight) Five other animals were treated with intravenous injections of propranolol (0 2 mg per kilogram of body weight) alone

Group B In the second group of experiments (Group B dogs with previously im

Table V 1 ffect of sodium ben oate on the ventricular fibrillation threshold in do.s with acute myocardial infarction (fourth postoperative day)*

Dog	Minutes after intravenous injection					
	0	15	30	45	60	90
1	0 50†	0 45	0 45	0 45	0 45	0 50
2	0 50	0 55	0 55	0 55	0 55	0 50
3	0 45	0 45	0 40	0 40	0 45	0 45
4	0 40	0 45	0 45	0 45	0 40	0 3
5	0 35	0 35	0 35	0 45	0 30	0 30
6	0 20	0 20	0 20	0 20	0 20	0 20
7	0 30	0 30	0 30	0 30	0 30	0 30
8	0 50	0 45	0 45	0 45	0 45	0 50
9	0 45	0 45	0 40	0 40	0 45	0 45
10	0 25	0 25	0 25	0 25	0 30	0 30

Time after drug admin (min)	No of dogs	Mean VFT (watt sec)	Mean difference from 0 time value	Variance	S E M	t	P
0	10	0 39					
15	10	0 39	0			0	N S‡
30	10	0 38	0 01	0 00155	0 012	0 833	N S
45	10	0 39	0			0	N S
60	10	0 385	0 005	0 00130	0 011	0 45	N S
90	10	0 385	0 005	0 00081	0 009	0 55	N S

Dosag 12.5 mg pe k logram f body ght
†VFT i w tt seco d
‡D ff ence not st t tically s fica t t th 5% le l on tl b f s t d comp so

was noted at about 45 and 60 minutes when the mean VFT decreased to 0 382 and 0 359 wsec from a control value of 0 09 wsec ($P < 0\ 001$) (see Tables I and II and Fig 2) Similar results were observed in Group B (normal dogs with previously implanted epicardial electrodes) (see Tables III and IV and Fig 3) There was a statistically significant decrease in ventricular fibrillation threshold at 15 30 45 and 60 minutes with a maximum effect at about 45 and 30 minutes (9 6 and 9 2 Ma respectively from a control value of 14 6 Ma p < 0 001) There was no change in the control experiments (i e after the injection of sodium benzoate)

Dogs with experimental myocardial infarction (caffeine and control experiments) The results obtained in this group of dogs are

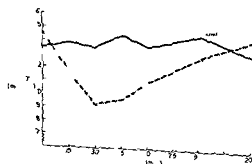


Fig 3 The effect of caffeine on the VFT of normal dog (impulses delivered through previously implanted epicardial electrodes) There is a decrease in VFT after caffeine administration while there is no change in the controls and in those treated with the combination of caffeine and practolol

*Table IV The effects of caffeine sodium benzoate on the VFT in normal dogs with bipolar implanted electrodes (third to seventh day after implantation)**

Dog	Minutes after intravenous injection						
	0	15	30	45	60	90	120
1	14†	13	—	10	15	15	15
2	13	9	8	10	8	13	12
3	16	9	11	10	11	11	11
4	15	15	6	12	12	15	13
5	10	8	6	6	8	10	10
6	17	17	14	14	13	17	19
7	16	16	12	10	14	11	14
8	15	5	5	5	6	17	17
9	12	12	9	9	8	8	11
10	8	12	12	10	14	18	20

Time after admin of caffeine (min)	No of dogs	Mean VFT (Ma)	Mean difference from 0 time value (Ma)	Variance	SEM	t	P
0	10	14.6					
15	10	11.6	3.0	12.8888	1.135	2.643	0.05
30	10	9.2	5.4	6.2800	0.836	6.459	0.001
45	10	9.6	5.0	6.0000	0.775	6.457	0.001
60	10	10.9	3.7	6.6777	0.817	4.579	0.01
90	10	13.5	1.1	6.5444	0.809	1.360	NS‡
120	10	14.2	0.4				NS

*Dosage 0.25 mg per kilogram of body weight
†VFT in milliamperes
‡Differences not statistically significant

2.5 msec in duration The VFT was determined by delivering gated impulses to the right ventricle through the previously implanted bipolar electrodes utilizing a method similar to that of Han[15] These impulses were programmed using a series of Tektronix waveform and pulse generators which trigger a Grass stimulator (model SD5) At every tenth heart beat this system delivers a series of rectangular pulses of 2.5 msec duration each at intervals of 10 msec The series of impulses starts immediately after the R wave and ends at the peak of the T wave adequately covering the vulnerable period The current in creased at increments of 1 Ma until ventricular fibrillation was observed (Fig 1) The current delivered to the dog was measured with a current probe amplifier and displayed on an oscilloscope Ten control and 10 caffeine experiments were performed on normal dogs In addition six experiments were done on animals treated by the combination of caffeine sodium benzoate (25 mg per kilogram of body weight) and practolol (0.6 mg per kilogram of body weight)

Results

Control and caffeine experiments on normal dogs In Group A (intact dogs) no change in the VFT was noted during the 90 minutes following the injection of sodium benzoate In contrast, after injection of caffeine sodium benzoate a significant decrease in the fibrillation threshold was noted at 15 30, 45, 60 and 90 minutes after the injection The maximum effect

*Table V Effect of sodium ben oate on the ventricular fibrillation threshold in dogs with acute myocardial infarction (fourth postoperative day)**

Dog	Minutes after intravenous injection					
	0	15	30	45	60	90
1	0 50†	0 45	0 45	0 45	0 45	0 50
2	0 50	0 55	0 55	0 55	0 55	0 50
3	0 45	0 45	0 40	0 40	0 45	0 45
4	0 40	0 45	0 45	0 45	0 40	0 35
5	0 35	0 35	0 35	0 45	0 30	0 30
6	0 20	0 20	0 20	0 20	0 20	0 0
7	0 30	0 30	0 30	0 30	0 30	0 30
8	0 50	0 45	0 45	0 45	0 45	0 50
9	0 45	0 45	0 40	0 40	0 45	0 45
10	0 25	0 25	0 25	0 25	0 30	0 30

Time after drug admin (min)	No of dogs	Mean VFT (watt sec)	Mean difference from 0 time value	Variance	S E M	t	P
0	10	0 39					
15	10	0 39	0			0	N S‡
30	10	0 38	0 01	0 00155	0 012	0 833	N S
45	10	0 39	0			0	N S
60	10	0 385	0 005	0 00136	0 011	0 45	N S
90	10	0 385	0 005	0 00081	0 009	0 55	N S

*Dosag 12.5 mg pe k l gram t body w ht
†VFT tt sec ds.
‡Diff nces t st t t cally g ifica t t th 5% le l on th b f f g i d mp so

was noted at about 45 and 60 minutes when the mean VFT decreased to 0 382 and 0 359 wsec from a control value of 0 509 wsec ($P < 0.001$) (see Tables I and II and Fig 2) Similar results were observed in Group B (normal dogs with previously implanted epicardial electrodes) (see Tables III and IV and Fig 3) There was a statistically significant decrease in ventricular fibrillation threshold at 15 30 45 and 60 minutes with a maximum effect at about 45 and 30 minutes (9 6 and 9 2 Ma respectively from a control value of 14 6 Ma $p < 0.001$) There was no change in the control experiments (i e after the injection of sodium benzoate)

Dogs with experimental myocardial infarction (caffeine and control experiments) The results obtained in this group of dogs are

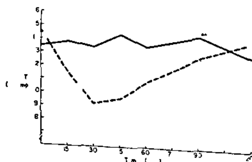


Fig 3 The effect of caffeine on the VFT of normal dogs (impulses delivered through previously implanted epicardial electrodes) There is a decrease in VFT after caffeine administration while there is no change in the controls and in those treated with the combination of caffeine and practolol

Table V Effect of sodium benzoate on the ventricular fibrillation threshold in dogs with acute myocardial infarction (fourth postoperative day)*

Dog	Minutes after intravenous injection					
	0	15	30	45	60	90
1	0 50†	0 45	0 45	0 45	0 45	0 50
2	0 50	0 55	0 55	0 55	0 55	0 50
3	0 45	0 45	0 40	0 40	0 45	0 45
4	0 40	0 45	0 45	0 45	0 40	0 35
5	0 35	0 35	0 35	0 45	0 30	0 30
6	0 20	0 20	0 20	0 20	0 20	0 20
7	0 30	0 30	0 30	0 30	0 30	0 30
8	0 50	0 45	0 45	0 45	0 45	0 50
9	0 45	0 45	0 40	0 40	0 45	0 45
10	0 25	0 25	0 25	0 25	0 30	0 30

Time after drug adm in (min)	No of dogs	Mean VFT (watt sec)	Mean difference from 0 time value	Variance	S E M	t	P
0	10	0 39				0	N S ‡
15	10	0 39	0			0 833	N S
30	10	0 38	0 01	0 00155	0 012	0	N S
45	10	0 39	0			0 45	N S
60	10	0 385	0 005	0 00136	0 011	0 55	N S
90	10	0 385	0 005	0 00081	0 009		

Dosage 12 5 mg per kilogram of body weight
†VFT in watt seconds.
‡Difference not statistically significant at the 5% level with the use of paired comparison.

was noted at about 45 and 60 minutes when the mean VFT decreased to 0 382 and 0 359 wsec from a control value of 0 509 wsec ($P < 0.001$) (see Tables I and II and Fig 2) Similar results were observed in Group B (normal dogs with previously implanted epicardial electrodes) (see Tables III and IV and Fig 3) There was a statistically significant decrease in ventricular fibrillation threshold at 15 30 45 and 60 minutes with a maximum effect at about 45 and 30 minutes (9 6 and 9 2 Ma respectively from a control value of 14 6 Ma $p < 0.001$) There was no change in the control experiments (i e after the injection of sodium benzoate)

Dogs with experimental myocardial infarction (caffeine and control experiments) The results obtained in this group of dogs are

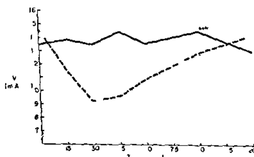


Fig 3 The effect of caffeine on the VFT of normal dogs (impulses delivered through previously implanted epicardial electrodes) There is a decrease in VFT after caffeine administration while there is no change in the controls and in those treated with the combination of caffeine and practolol

*Table VI. Effect of caffeine sodium benzoate on the ventricular fibrillation threshold in dogs with acute myocardial infarction (fourth postoperative day)**

Dog	Minutes after intravenous injection					
	0	*15*	*30*	*45*	*60*	*90*
1	0 40†	0 30	0 25	0 25	0 20	0 30
2	0 25	0 20	0 25	0 30	0 30	0 30
3	0 50	0 35	0 30	0 30	0 30	0 30
4	0 40	0 35	0 30	0 30	0 30	0 35
5	0 30	0 25	0 30	0 30	0 25	0 35
6	0 40	0 35	0 25	0 20	0 20	0 20
7	0 60	0 60	0 35	0 35	0 30	0 35
8	0 40	0 40	0 60	0 55	0 60	0 55
9	0 35	0 35	0 40	0 45	0 45	0 45
10	0 30	0 25	0 30	0 30	0 35	0 35
11	0 60	0 60	0 40	0 35	0 35	0 35

Time after admin of caffeine (min)	*No of dogs*	*Mean VFT (watt sec)*	*Mean difference from 0 time value (watt sec)*	*Variance*	*S E M*	*t*	*P*
0	11	0 409					
15	11	0 364	−0 045	0 0022275	0 0142	3 169	<0 01
30	11	0 327	−0 082	0 00464	0 0206	3 981	<0 01
45	11	0 323	−0 086	0 007046	0 0253	3 399	<0 01
60	11	0 314	−0 095	0 009228	0 0289	3 287	<0 01
90	11	0 332	−0 077	0 008182	0 0273	2 825	<0 01

*Dosage 25 mg per kilogram of body weight
†VFT in watt seconds.

given in Tables V and VI and in Fig 2. In the control experiments no significant change in the VFT occurred whereas after caffeine administration the VFT was significantly decreased at 15, 30, 45, 60 and 90 minutes ($p < 0.01$). The maximum effect was noted at 45 and at 60 minutes when the mean VFT decreased to 0 323 and 0 314 w sec, respectively from a control value of 0 409 w sec. As expected the VFT before the injection of caffeine (0 409 w sec) was lower in dogs with acute myocardial infarction than in normal dogs (0 509 w sec).

Administration of the combinations of caffeine and propranolol and caffeine and practolol. As seen in Table VII propranolol in the dose of 0 2 mg per kilogram of body weight did not significantly affect the VFT. However, when administered simultaneously with caffeine, it prevented the caffeine induced decrease in VFT. This is shown in Table VIII, where no change in VFT is observed after the administration of the propranolol caffeine combination (Fig 4). Similarly no change in VFT was observed in the dogs treated with caffeine and practolol (Table IX).

Discussion

1 *Values of ventricular fibrillation threshold.* The values of VFT obtained in Group A (intact dogs) are in the range reported by Lown, Kleiger and Williams[14] who employed a similar method. Those obtained in Group B (dogs with previously implanted electrodes) were similar to the results of Han[15] who utilized a similar technique. There was no change in the VFT in the control experiments. Prolonged anesthesia and repeated determinations did not significantly affect the VFT in the control experiments. This has been reported by

*Table VII Effect of propranolol on the ventricular fibrillation threshold in intact normal dogs**

Dog	Minutes before (−) and after (+) intravenous injection						
	−15	0	+15	+30	+45	+60	+90
1	0 ,0†	0 ,0	0 80	0 80	0 0	0 60	0 60
2	0 50	0 50	0 50	0 40	0 50	0 ,0	0 40
3	0 35	0 35	0 35	0 35	0 35	0 35	0 35
4	0 80	0 80	0 80	0 70	0 90	0 80	0 90
5	0 35	0 35	0 35	0 35	0 40	0 35	0 30

Time after adm n of propranol l (min)	No of dogs	Mean VFT (watt sec)	Mean difference from 0 time control (watt sec)	Variance	S E M	t	P
0	5	0 54					
15	5	0 56	+0 02	0 00 0	0 02	1 0	N S.‡
30	5	0 52	−0 02	0 0070	0 038	0 526	N S.
45	5	0 57	+0 03	0 0020	0 02	1 50	N S
60	5	0 52	−0 02	0 0070	0 02	1 0	N S.
90	5	0 51	−0 03	0 0070	0 038	0 789	N S

Dosage 0 mg pe k l g m f body gl t
†VFT n tt seco ds.
‡ D ff ces not t is i ally fic t

others[16,17] Although some variation in the control values of VFT between the groups of experiments was observed these differences are not statistically significant

2 *The effect of caffeine on the VFT of normal dogs* In contrast to the control experiments caffeine produced a significant decrease in the VFT which lasted at least 60 minutes It is of interest that similar results were obtained with both techniques (Groups A and B) This is important since the accurate determination of VFT is relatively difficult as it is affected by many variables and each technique is characterized by specific advantages and disadvantages[18,21] The closed chest technique with impulses delivered through the chest wall of the intact animal involves the problem of the chest wall impedance which might vary from dog to dog or from moment to moment on the same dog but this technique does offer the advantage of using intact animals without previous operations On the other hand the technique utilizing implanted electrodes bypasses the problem of variable impedance as well as the open chest problem but introduces the factor of electrode implantation clot formation or myocardial reaction around the implanted electrode Open-chest techniques were avoided in this study since they introduce important physiological alterations

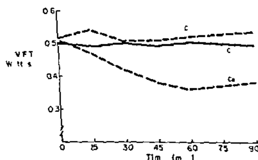


Fig 4 The effect of propranolol on the caffeine induced decrease of VFT in normal dogs Note that there is no decrease in VFT after the administration of the combination of caffeine and propranolol

3 *Effect of caffeine on the VFT of dogs*

*Table VIII. Effect of the combination of caffeine sodium benzoate plus propranolol on the ventricular fibrillation threshold in intact normal dogs**

Dog	Minutes before (−) and after (+) intravenous injection						
	−15	0	+15	+30	+45	+60	+90
1	0 30†	0 30	0 35	0 35	0 35	0 35	0 35
2	0 45	0 45	0 45	0 45	0 50	0 45	0 45
3	0 30	0 30	0 30	0 25	0 30	0 30	0 30
4	0 75	0 70	0 75	0 70	0 75	0 75	0 75
5	0 80	0 80	0 80	0 80	0 80	0 80	0 80
6	0 70	0 70	0 80	0 70	0 60	0 60	0 60
7	0 60	0 60	0 70	0 60	0 60	0 60	0 60
8	0 40	0 40	0 30	0 30	0 40	0 40	0 40
9	0 35	0 35	0 40	0 40	0 40	0 40	0 40

Time after drug admin (min)	No of dogs	Mean VFT (watt sec)	Mean difference from 0 time control (watt sec)	Variance	S E M	t	P
0		0 511					
15	9	0 539	+0 028	0 00382	0 0205	1 356	N S‡
30	9	0 506	0 005				N S
45	9	0 506	0 005				N S
60	9	0 516	0 005				N S
90	9	0 516	0 005				N S

*Dosage caffeine sodium benzoate = 25 mg per kilogram of body weight dosage propranolol = 0 2 mg per kilogram of body weight
†VFT in watt seconds
‡Differences not statistically significant

with acute myocardial infarction The VFT of dogs with acute myocardial infarction was lower than that of normal dogs During the fourth day after coronary ligation the heart muscle manifests the characteristic pathology of acute myocardial infarction and one would anticipate that the VFT would be below normal These results are in agreement with observations of others who observed significant decrease in the VFT in ischemic hearts [15,22,23] In dogs with acute myocardial infarction the VFT which had been lowered because of ischemia was further decreased by caffeine This might conceivably facilitate the development of spontaneous ventricular fibrillation (and sudden death) when myocardial ischemia and caffeine are operating simultaneously

4 *The effect of the combination of caffeine and beta blocking agents on the VFT* As has been reported by others, propranolol (0 2 mg per kilogram of body weight) did not affect the VFT to any significant degree However propranolol probably prevented the caffeine induced decrease in VFT when administered simultaneously with it This effect is related to the beta blocking action of propranolol rather than to its quinidine like effect since similar results were obtained by the use of practolol and pure beta blocking agents which do not have significant direct action on the cardiac muscle The dogs receiving this combination behaved similarly to the controls These results would suggest that the effect on the fibrillation threshold may be mediated directly or indirectly through the adrenergic mechanism It has been shown that sympathetic nerve stimulation results in an accentuation of asynchrony of recovery of the myocardial excitability leading to a marked decrease in VFT Exogeneous catecholamine administration has the same

*Table IX. Effect of the combination of caffeine sodium benzoate plus practolol on the ventricular fibrillation threshold in normal dogs with bipolar implanted electrodes (third to seventh day after implantation)**

Dog	Minutes after intravenous injection						
	0	15	30	45	60	90	120
1	9†	10	11	11	10	10	11
2	11	11	10	9	9	9	9
3	12	12	12	12	12	11	11
4	8	7	7	8	7	8	11
5	12	11	13	13	12	12	10

Time after drug admin (min)	No. of dogs	Mean VFT (Ma)	Mean difference from 0 time value (Ma)	Variance	S.E.M.	t	P
0	5	10.4					
15	5	10.2	0.2	0.70	0.38	0.53	N.S.‡
30	5	10.6	0.2	1.70	0.59	0.33	N.S.
45	5	10.6	0.2	2.20	0.67	0.30	N.S.
60	5	10.0	0.4	1.30	0.51	0.78	N.S.
90	5	10.0	0.4	1.30	0.51	0.78	N.S.
120	5	10.4	0.0				N.S.

*Dosage of caffeine sodium benzoate = 25 mg per kilogram of body weight; dosage of practolol = 0.6 mg per kilogram of body weight.
†VFT in milliamperes.
‡Difference not statistically significant at the 5% level on the basis of a paired comparison.

effect in the initial 5 to 10 minutes after administration.[11-23] Since caffeine results in stimulation of adrenergic activity,[5,6] it may decrease the VFT through this mechanism.

5. *Mechanism of decrease of VFT by caffeine.* Caffeine has many pharmacologic effects which might be anticipated to affect the VFT. These include adrenergic stimulation, direct myocardial stimulation with increases in cardiac output, contractility, cardiac work, oxygen uptake, and coronary A-V difference. Agents such as catecholamines and digitalis[11-26] producing similar effects are usually associated with depression of the VFT. A mechanism by which caffeine decreases the VFT is the adrenergic stimulation mentioned above. The prevention of the caffeine-induced decrease in VFT by propranolol or practolol supports this view. The elevation of serum free fatty acid levels after caffeine administration may contribute to this effect.[13] A relation between serum free fatty acids and arrhythmias and death after acute myocardial infarction has been reported by a group of investigators. In addition, caffeine increases intracellular 3′,5′-cyclic AMP by inhibiting phosphodiesterase, elevates serum adrenal steroid levels, and probably directly affects the action potential.[10,27] The factors mentioned above, singly or collectively, could result in facilitating the development of re-entry which under certain conditions might lead to ventricular fibrillation.

The effect of caffeine on calcium may also play a role. Caffeine decreases the calcium binding which may lead to an increased concentration of calcium in the cell.[9] Calcium was found to cause a reduction in the maximum rate of rise of the action potential, which can slow the velocity of impulse propagation and shortens the refractory period. These effects would favor the development and maintenance of re-entrant excitation and possibly

fibrillation [8] Under certain *conditions* calcium may initiate ventricular fibrillation [12]

Summary

The effect of caffeine administration on the VFT was studied in normal dogs and in dogs with acute myocardial infarction Two methods were employed the first utilized impulses delivered through the chest wall of the intact animal and the second used epicardial electrodes implanted four to seven days previously

Caffeine produced a decrease in VFT starting 15 minutes after injection and this effect lasted about 60 minutes

Propranolol and practolol prevented the caffeine induced decrease of VFT

In dogs with acute myocardial infarction the VFT was lower than normal and was further decreased after caffeine administration

Although the dose of caffeine utilized in this study is higher than that usually consumed by humans it is possible that lower doses have a significant effect when combined with other agents The various factors that affect the VFT which might have arrhythmogenic effects are presently under study There is suggestive evidence that a number of factors might be cumulatively significant in susceptible individuals These factors may include cigarette smoking various degrees of stress effects due to anxiety and exertion various drugs—i e, isoproterenol ephedrine and several sympathomimetic agents and caffeine The role of caffeine requires further study in this regard

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Antinuclear antibody response to procainamide in man and laboratory animals

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In the past ten years a clinical syndrome with features of systemic lupus erythematosus (SLE) including positive tests for LE cells and antinuclear antibody has become recognized as an adverse side effect of procainamide.[1] The use of procainamide for the treatment of cardiac arrhythmias, particularly those occurring after myocardial infarction, has resulted in the syndrome of "procainamide lupus" becoming more frequently recognized. The syndrome has features of an autoimmune process but its mode of induction is unknown. We report a prospective study on the induction of antinuclear antibody (ANA) in patients treated with procainamide. Laboratory animals were given procainamide for 6 months or longer. Although over a quarter of the treated patients developed high titer ANA, none of the animals tested responded in this manner.

Materials and methods

Patients. The potential patients, 199 in number, were those admitted to a coronary care unit over a 12 month period, and those who received procainamide as therapy for cardiac arrhythmias, 48 in number, entered the study. Those from whom at least three samples of sera were available at minimum intervals of one month, comprised the case material of this study. These 29 comprised 25 men and four women aged from 31 to 76 years; from these 160 sera were tested, and sera were available from 15 before procainamide was started.

Animals. Ten rabbits, 10 guinea pigs, 20 Wistar rats, 40 Hall Institute (HI) outbred closed colony mice and 20 inbred New Zealand Black (NZB) mice were given procainamide by subcutaneous injection three times a week for 30 weeks. The NZB mice were known to develop positive tests spontaneously for antierythrocyte and antinuclear autoantibodies; they were included to test for enhanced development of ANA by procainamide. Other groups of animals were outbred and from closed colonies. Animals within each group were of the same age and the groups, other than the guinea

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pigs which were males continued in equal number of males and females The dose of procainamide injected subcutaneously was equivalent to 30 times the conventional daily dose of 2 Gm for an average 70 kilogram man converted to grams per kilogram of body weight of the animal but the drug was given only three times per week instead of daily No adjustment was made for gain in weight of the animals during the experiment

Sera tested for antinuclear antibodies were obtained before procainamide was commenced and thereafter at 10 20 and 30 weeks two of three of the surviving animals were killed on completion of the 30 week course of procainamide and the remainder six months later Tissues from kidney heart lung and skin were processed for examination for deposited globulins by immunofluorescence tissues from kidney thymus lung heart liver spleen pancreas stomach duodenum and skin were processed for histological examination

Controls Controls for patients were blood donors and members of elderly citizens clubs matched for age and sex with the patients and not receiving procainamide Controls for mice were 20 HI mice and 10 NZB mice matched for age and sex with the test mice and given 0 1 ml of saline subcutaneously three times a week for 30 weeks

Tests for antinuclear antibodies Sera from patients and all animals were tested by immunofluorescence for ANA reactive with granulocyte and lymphocyte nuclei in smears of human blood[7] and sera from guinea pigs and mice were tested also for ANA using air dried 4μ frozen sections of rat liver Rabbit antiserum to human globulin and goat antiserum to rabbit globulin were prepared in our laboratory[8] and conjugated with fluorescein isothiocyanate (FICT) and goat antisera to guinea pig globulin mouse globulin and rat globulin conjugated with FICT were obtained from the Nutritional Biochemical Corporation U S A Sera containing antinuclear antibodies were titrated in tenfold dilutions of 0 05 per cent bovine serum albumin in phosphate buffered saline pH 7 3 Blood samples from four patients with high titer ANA reactions were tested for LE cells by the method of Magath and Winkle[4]

Absorption studies Samples of human serum (0 2 ml) which contained ANA in high titer were mixed with amounts of procainamide varying from 1 to 100 mg held at 4 C for 24 hours examined for precipitation and centrifuged at 80 000 g the sera then were tested for ANA

Results

Patients Antinuclear antibodies were detected in 24 of 29 (83 per cent) of the patients given procainamide in titers up to 1 000 (Table 1) and in six of 29 (20 per cent) age sex matched controls in titers up to 10 A titer of ANA of 10 or greater was obtained in 18 of 29 (62 per cent) of the patients and in two of 29 (7 per cent) of controls and in six patients but none of the controls the titer was equal to or greater than 100 (Fig 1) Blood from four patients with a high titer of ANA (≥100) was tested for LE cells and gave a positive result The occurrence of ANA in patients given procainamide was not directly dependent on the dose nor on the age of the patient Conversion occurred three to six months after commencement of treatment In four patients tested serially after procainamide was stopped the titer of ANA fell

Of the 160 sera tested 89 gave a positive test for ANA and 68 (76 per cent) gave the same titer with nuclei of lymphocytes and granulocytes Pretreatment serum from two patients reacted only with granulocyte nuclei but during treatment reacted equally with both granulocyte and lymphocyte nuclei to titers of 10 and 100

Animals

MORBIDITY AND MORTALITY All animals injected with procainamide developed indolent ulcers at the site of injection and one rabbit developed generalized dermatitis There was a high mortality rate while procainamide was being given in the rabbits (7 of 10) guinea pigs (4 of 10) the HI mice (31 of 40) and the NZB mice (20 of 20) but not in the rats (1 of 20) The mortality rate in the control mice given saline for a comparable period was lower for the HI mice being 2 of 20 and the NZB mice 5 of 10 Some animals died immediately after injection and others were found dead in their cages The cause of death was not determined

ANTINUCLEAR ANTIBODIES AND IMMUNE

Table I Peak titer of antinuclear antibodies in patients given procainamide (P A)

Age (yr)	Daily dose (Gm)	Duration of P A (mo)	Peak titer	Time (mo)*
Men				
59	2 0	3	0	
58	2 0	3	0	
	0 25	3		
62	2 0	6	0	
		12		
43	2 0	30	0	
50	2 0	3	1	3
55	2 0	6	1	3
39	2 0	7	1	5
50	1 0	6	1	3
	2 0	3		
56	2 0	9	1	9
55	2 0	12	1	9
31	2 0	3	10	3
60	2 0	5	10	5
58	2 0	1		
	1 0	5	10	3
16	1 5	1		
	0 75	2	10	1
	0 5	2		
(76)	2 0	6	10	2
62	1 5	4	10	5
	2 0	4		
72	2 0	9	10	6
65	1 0	9	10	7
44	2 0	9	10	6
46	2 0	9	10	5
65	2 0	11	10	11
45	2 0	6	100	6
71	2 0	9	100	4
54	1 0	9	100	5
72	2 0	7	1 000	7
Women				
35	1 5	6	0	
76	1 0	9	10	3
53	1 5	7	100	7
54	1 5	18	1 000	18

*Time to reach peak titer

DEPOSITS None of 10 rabbits and 20 rats given procainamide had a positive ANA test Two of 10 guinea pigs had a transient weak "speckled" reaction The incidence of positive tests before and during administration of procainamide was, for the 40 HI mice 5 and 66 per cent and for the 20 NZB mice, 0 and 50 per cent However the occurrence of ANA in these mice could not be attributed to procainamide in that the incidence of positive tests for ANA during administration of saline in control HI mice rose similarly from 10 to 70 per cent and in control NZB mice from nil to 87 per cent (Table II) The kidneys of three guinea pigs examined showed patchy, linear deposits of globulin of uncertain significance in the glomeruli The kidneys of seven HI mice and four NZB mice injected with procainamide showed granular deposits in glomeruli however similar deposits were present in the glomeruli of the control 16 HI mice and 1 NZB mouse, indicative of the spontaneous occurrence of "immune complex" nephritis in both the experimental and control groups The heart and lungs of all animals tested were free of immune deposits

Table II. Serum antinuclear antibodies (ANA) in animals treated with procainamide (PA) and their controls

Animal	No. ANA + ve/No. living				
	Before PA	During PA			After PA 56 weeks
		10 weeks	20 weeks	30 weeks	
Rabbit (10)	0/10	0/9	0/5	0/3	NT
Guinea pig (10)	1/10	2/9	0/7	0/6	NT
Rats (20)	0/20	0/20	0/ 0	0/10	NT
HI mice (40)	7/40	9/40	11/14	6/9	NT
Control (20)	2/20	10/20	11/18	17/17	14/16
NZB mice (20)	0/20	1/10	2/6	0	0
Control (10)	0/10	4/10	7/8	3/5	1/1

NT = Not tested.

HISTOLOGY. Autopsies were performed on 26 of 40 HI mice, 6 of 20 NZB mice, 14 of 20 rats, 5 of 10 guinea pigs, and 4 of 10 rabbits given procainamide.

Mice. Membranous glomerular lesions were seen in seven HI mice and two NZB mice and cortical lymphoid aggregates in six HI mice and one NZB mouse. These changes were equivalent to those seen in controls injected with saline. Changes in the liver consisting of hepatic cell steatosis and vacuolation and portal infiltrates seen in 11 HI mice and 4 NZB mice were considered to be nonspecific, and the pulmonary changes of alveolar thickening and/or lymphoid foci in 19 HI mice and four NZB mice were attributed to infection, but tissues were not cultured.

Rats. In all 14 there were varying degrees of pulmonary alveolar thickening, fibrosis, or consolidation attributed to infection; other organs were unremarkable.

Guinea pigs. In four there were collections of lymphoid cells in the kidney and lungs and fatty vacuolation in the liver; these changes were considered to be nonspecific.

Rabbits. There were in the four rabbits examined occasional lymphoid foci in the kidney, marked pulmonary alveolar thickenings, and collections of eosinophilic leukocytes in various organs.

The glomerular lesions in the mice could



Fig. 1. Antinuclear antibodies were detected in 24 of 29 patients given procainamide and 6 of 29 matched controls. Peak titers of 10 or greater were detected in 18 patients and the 4 patients with high titers who were tested for LE cell all gave a positive result (•).

be related to spontaneously occurring autoimmune (antinuclear) reactions which develop in both NZB and HI mice. In none of the other species examined were there changes suggestive of lesions of human lupus erythematosus.

Absorption studies. No precipitin reaction was detected between human serum containing procainamide induced antinuclear

antibody and procainamide and there was no reduction in titer of antinuclear antibody after positively reacting sera were absorbed with procainamide

Discussion

Two surveys in Sweden and New York give a prevalence of SLE in the population of about one per 10 thousand[6] it can therefore be considered a rare disease in human beings The occurrence of a lupus like syndrome in patients treated with procainamide is generally considered to be more frequent than this but a precise figure is not known because no data are available for a large population at risk, moreover there would be problems of disease definition in such a study because drug induced lupus is milder than the natural disease However, if the occurrence of ANA in high titer be taken as the 'prodrome of drug induced lupus then serological studies on groups treated with procainamide give some indications of the risk, the higher proportion (83 per cent) with ANA in our study than in others (50 to 60 per cent)[7, 9] may be attributed to the source of nuclei we used to detect ANA

Most of the patients who developed ANA after procainamide did so within three to six months six had peak titers of 100 to 1 000 and four had a positive test for LE cells Whether differences in time of onset and titer of antinuclear antibody were related to differing rates of acetylation of the drug[10] was not ascertained in our study It might be said that the few high titer reactors to procainamide in our series would be equivalent to those hypertensive subjects identified by Worlledge and associates[11] as being highly sensitive to the immunological side effects of alpha methyldopa With this latter drug some 20 per cent of patients developed a positive Coombs test which was dose and time dependent but no hemolysis while a few became 'exquisitely sensitive and presented acutely with overt hemolysis

None of the animals we studied developed evidence of an autoimmune response to procainamide despite parenteral administration for 30 weeks, nor was there augmentation of the spontaneous development of antinuclear antibodies in mice A finding of some incidental interest was the high spontaneous incidence of ANA in our outbred Hall Institute mice a property hitherto studied mostly in the 'New Zealand' strains[1] It appears that a predisposition to develop autoimmune reactions to nuclear antigens may hold for mice in general and, as well, in some strains a drug hydralazine, has enhanced the natural occurrence of antinuclear reactions[13]

Our failure to induce an analogue of human procainamide lupus in various animals is in keeping with findings of Dubois and Strain[14] who despite assiduous efforts likewise failed with small laboratory animals mongrel dogs a minipig and a *Macaca fusata* monkey given prolonged and high doses of the drug together with solar exposure We endorse Dubois speculation "whether etiologic studies of lupus in the animal are truly applicable to the human form of the disease

It is difficult to envisage how drugs for example alpha methyldopa and procainamide cause production of autoimmune-type antibodies In particular neither our present investigations nor those by Worledge and colleagues[11] on effects of alpha methyldopa, nor those by Ellman and colleagues[15] with hydralazine in guinea pigs give the slightest evidence that the drug acts as a hapten or in any way influences the specificity of the resulting autoantibodies

We therefore turn to speculations by Burnet[16] about the nature of the alpha methyldopa effect which have recently been applied also to the procainamide results[17] These are based on his concept that soon after differentiation all immunocytes are subject to a censorship which eliminates functionally or physically those cells which react significantly with accessible body antigens Where the receptor combining site has a borderline reactivity with a 'self antigenic determinant the 'decision' between elimination and proliferation given at first contact will be influenced by many factors These include genetic ones associated with a heightened resistance to tolerogenic effects as in NZB mice[18] the concentration and mode of presentation of the antigen which can be combined as effective concentration, any relevant somatic mutation which may have occurred

Table III. Postulated determinants of origin of pathogenic forbidden clones in autoimmune disease and drug-induced autoimmune syndromes

Mutation		Drug (alpha methyldopa procainamide hydralazine)	Result
Germ line	Somatic		
+	+ +	−	SLE or AHA*
+	+	−	Positive antinuclear antibody or Coombs test, no disease
−	+ +	−	Positive antinuclear antibody or Coombs test, no disease
−	+	+	Positive antinuclear antibody or Coombs test, no disease
−	+ +	+	Mild disease
+	+	+	SLE or AHA

*SLE, systemic lupus erythematosus; AHA, autoimmune hemolytic anemia.

in individual cell lines, *and any significant influence of a drug on the microenvironment in which the decision is made.*

In the absence of a drug effect one might postulate that the pathogenic clone in a patient with clinical autoimmune disease and autoantibody has three genetic changes a, b, c not present in immunocytes of a normal individual. The mutations may be germ line or somatic—one, for example a, is probably always of germ line origin and others, b and c, could be somatic (Table III). There seems required a minimum of three functional changes but the possibility exists that the same position might be reached in a variety of ways, e.g., with more than three genetically based changes of lesser extent, or with internal environmental factors playing a greater part.

In Table III each of the mutations is regarded as equivalent and indicated as +. The effect of the drug, also shown as +, can be regarded either as (1) inducing a phenocopy of a somatic mutation or (2) shifting the level of decision between tolerance and proliferation. Such a formulation is obviously valid only if Burnet's stochastic "forbidden clone" approach to the interpretation of autoimmune disease is accepted; however, it is not considered easy to offer any alternative persuasive interpretation of autoimmunity in terms of either the viral infection or altered antigen theories of autoimmune disease.

It may be of more than passing interest that the three major drugs which are presumed to have this significant influence on the microenvironment in which tolerance-immunity decisions are made are each effective in the therapy of hypertensive cardiovascular disease: alpha methyldopa, procainamide, and hydralazine.

Summary

A prospective study of 29 patients given procainamide showed that 83 per cent of patients vs. 20 per cent of 29 age- and sex-matched controls gave positive tests for antinuclear antibody (ANA). Six patients (20 per cent), four of whom had LE cells, developed high titer ANA of the lupus-type. The induction of ANA was independent of the dose of procainamide given, the duration of treatment, and the age of the patient. Titers fell after procainamide was discontinued.

ANA could not be induced in rabbits, guinea pigs, rats, and mice injected with procainamide for 30 weeks, nor was there enhancement of the naturally occurring age-related development of ANA in mice.

The development of ANA in high titer, which we take as the "prodrome" of drug-induced lupus erythematosus, can be expected in one in five patients treated with procainamide, irrespective of the dose given. Our understanding of the mechanism of "drug-induced" forms of lupus may be furthered more by studies in man than in the apparently resistant laboratory animal.

antibody and procainamide, and there was no reduction in titer of antinuclear antibody after positively reacting sera were absorbed with procainamide

Discussion

Two surveys in Sweden and New York give a prevalence of SLE in the population of about one per 10 thousand[5,6] it can therefore be considered a rare disease in human beings The occurrence of a lupus like syndrome in patients treated with procainamide is generally considered to be more frequent than this, but a precise figure is not known because no data are available for a large population at risk moreover there would be problems of disease definition in such a study because drug induced lupus is milder than the natural disease However if the occurrence of ANA in high titer be taken as the "prodrome" of drug induced lupus then serological studies on groups treated with procainamide give some indications of the risk the higher proportion (83 per cent) with ANA in our study than in others (50 to 60 per cent)[7,9] may be attributed to the source of nuclei we used to detect ANA

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Case reports

Diagnosis and treatment of a case of recurrent ventricular tachycardia

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The deficiencies of standard electrocardiographic and clinical criteria in distinguishing ventricular tachycardia from junctional or supraventricular tachycardia with aberrant QRS complexes have recently been emphasized.[1,2] Because of differences in prognostic implications and in medical and surgical treatments of these conditions, this distinction has considerable practical importance. We recently have studied a patient suffering from recurrent refractory tachycardia in whom the techniques of atrial recording, competitive atrial pacing, and Holter Recorder monitoring were helpful in establishing a diagnosis of ventricular tachycardia. An accurate diagnosis in this patient permitted subsequent major diagnostic and therapeutic procedures which resulted in control of his arrhythmia.

Case report

R. Z., SUH No. 33-30-54, a 62 year old Caucasian man, entered Stanford University Hospital for the first time on July 24, 1970, because of recurrent tachycardia. The patient had been well until 1959 when he suffered an inferior myocardial infarction. Following an uneventful recovery, he did well until 1961, when he developed paroxysmal tachycardia with aberrant QRS complexes which was terminated by intravenous vasopressors. He was begun on quinidine. Aside from an episode of chest pain diagnosed as pericarditis and treated with a course of steroid in 1962, he did well until July 26, 1969, when tachycardia recurred. An electrocardiogram (ECG) taken at that time demonstrated a ventricular rate of 194 per minute and wide aberrant QRS complexes (Fig. 1, A). A diagnosis of ventricular tachycardia was made, and the patient was cardioverted to normal sinus rhythm (Fig. 1, B). On Aug. 2, 1969, a tachycardia recurred. In comparison with the previous tachycardia, the rate was slightly slower at 180 per minute, and the QRS complexes had a different configuration (Fig. 1, C). This tachycardia was converted to normal sinus rhythm by the administration of intravenous neosynephrine, and subsequent arrhythmias were thought to be supraventricular tachycardias with aberration. Despite treatment with a variety of antiarrhythmic agents, including procainamide, propranolol, digoxin, diphenylhydantoin, and quinidine, alone and in combinations, adequate prevention of this recurrent arrhythmia was not achieved. From August, 1969, to July, 1970, he had 11 documented episodes of tachycardia. With one exception, which was converted with neosynephrine and had an ECG pattern identical to that shown in Fig. 1, C, all these arrhythmias were resistant to vagal maneuvers, required electrical reversion, and had the same ECG pattern

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Case reports

Diagnosis and treatment of a case of recurrent ventricular tachycardia

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The deficiencies of standard electrocardiographic and clinical criteria in distinguishing ventricular tachycardia from junctional or supraventricular tachycardia with aberrant QRS complexes have recently been emphasized[1,2] Because of differences in prognostic implications and in medical and surgical treatments of these conditions this distinction has considerable practical importance We recently have studied a patient suffering from recurrent refractory tachycardia in whom the techniques of atrial recording competitive atrial pacing and Holter Recorder monitoring were helpful in establishing a diagnosis of ventricular tachycardia An accurate diagnosis in this patient permitted subsequent major diagnostic and therapeutic procedures which resulted in control of his arrhythmia.

Case report

R. Z. SUH No 33 30-54 a 6 year old Caucasian man entered Stanford University Hospital for the first time on July 24 1970 because of recurrent tachycardia. The patient had been well until 1959 when he suffered an inferior myocardial infarction Following an uneventful recovery he did well until 1961 when he developed paroxysmal tachycardia with aberrant QRS complexes which was terminated by intravenous vasopressors He was begun on quinidine Aside from an episode of chest pain diagnosed as pericarditis and treated with a course of steroids in 1967 he did well until July 26 1969 when tachycardia recurred An electrocardiogram (ECG) taken at that time demonstrated a ventricular rate of 194 per minute and wide aberrant QRS complexes (Fig 1 A) A diagnosis of ventricular tachycardia was made and the patient was cardioverted to normal sinus rhythm (Fig 1 B) On Aug 2 1969 a tachycardia recurred In comparison with the previous tachycardia the rate was slightly slower at 180 per minute and the QRS complexes had a different configuration (Fig 1 C) This tachycardia was converted to normal sinus rhythm by the administration of intravenous neosynephrine and subsequent arrhythmias were thought to be supraventricular tachycardias with aberration. Despite treatment with a variety of antiarrhythmic agents including procainamide propranolol digoxin diphenylhydantoin and quinidine alone and in combinations adequate prevention of this recurrent arrhythmia was not achieved From August 1969 to July 1970 he had 11 documented episodes of tachycardia With one exception which was converted with neosynephrine and had an ECG pattern identical to that shown in Fig 1 C all these arrhythmias were resistant to vagal maneuvers required electrical reversion and had the same ECG pattern

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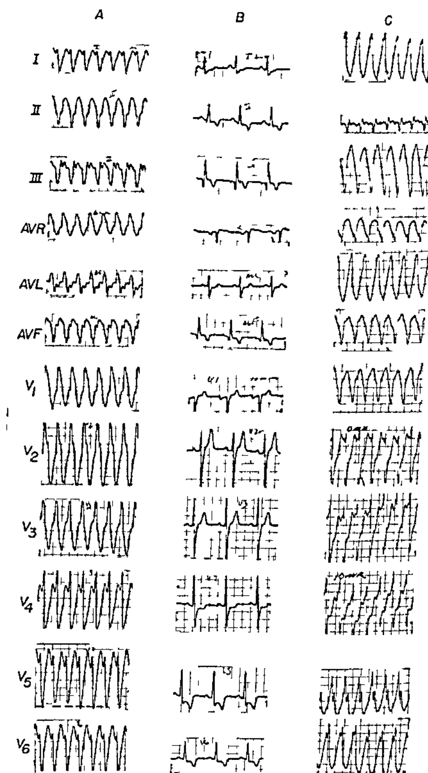


Fig 1 Standard 12 lead electrocardiographic tracings of the patient during tachycardia (A and C) and during normal sinus rhythm (B) (A) was the most common tachycardia pattern with a rate of 194 per minute and QRS of 0 16 sec No P waves are discernible Pattern (C) occurred three times and on two occasions was converted to normal sinus rhythm by intravenous neosynephrine administration The rate in (C) is 180 per minute Tracing (B) shows evidence of an old inferior infarction and an intraventricular conduction defect with a QRS of 0 10 sec

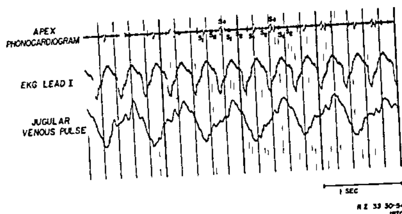


Fig 2 Simultaneous apex phonocardiogram, ECG Lead I and jugular venous pulse tracing Note the split first heart sound and the large A wave and S_4 which appear with every other beat The first component of S_1 is louder when preceded by atrial contraction.

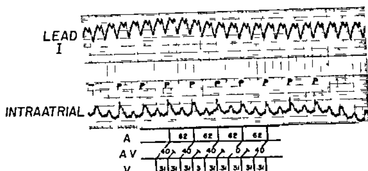


Fig 3 This record shows simultaneous standard ECG Lead I (upper tracing) and unipolar right atrial cavitary lead (lower tracing) *P* denotes atrial depolarization Retrograde conduction to the atria is demonstrated with 2 1 block In the diagram below the lower tracing 1 denotes atrial depolarization *A* 1 the atrioventricular conduction, and 1 the onset of ventricular depolarization In the diagram a ventricular focus is indicated However this tracing is also compatible with a junctional pacemaker with retrograde 2 1 block and aberration of the QRS complex (see text)

as shown in Fig 1 *A* The patient tolerated these tachycardias well with a slight fall in blood pressure and lightheadedness but without symptoms of angina or congestive heart failure He was referred to Stanford Medical Center because of development of more frequent episodes of tachycardia.

On physical examination the blood pressure was 90 50 pulse 190 to 200 and regular respirations 16 In the neck regular jugular venous pulsations at half the heart rate were visible although the venous pressure was normal The heart size was normal There was a regular variation of intensity of heart sounds which was difficult to interpret because of the rapid rate A simultaneous ECG jugular venous pulse tracing and apex phonocardiogram taken during the tachyarrhythmia demonstrated a prominent A wave and S occurring with every other QRS complex (Fig 2) The ECG on admission was identical to that shown in Fig 1 *A* He failed to respond to carotid sinus pressure neosynephrine infusion and edrophonium He was cardioverted but his tachycardia soon recurred

In an attempt to establish the mechanism of the tachycardia the patient was taken to the Cardiac Catheterization Laboratory where under fluoroscopic control an NBIH bipolar electrode catheter was introduced into the right atrium. The unipolar right atrial electrogram revealed retrograde 2 1 block with either a ventricular focus or a junctional focus with aberration of the QRS complex (Fig 3) Pacing of the atrium was then attempted with a Medtronic battery powered unit as described by Farley and Goldstein[3] but atrial capture was not possible at the maximum pacemaker rate which was less than that of the tachycardia A Grass Stimulator with a stimulus isolation unit was then used to pace at a rate of 204 per minute faster than the tachycardia rate of 194 per minute (Fig 4) After three

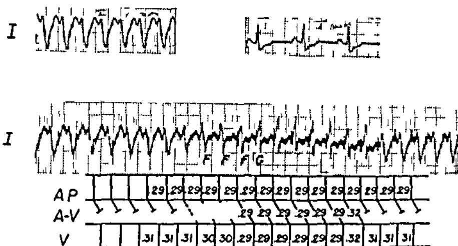


Fig 4 The upper records show the standard Lead I ECG tracing during tachycardia (left) and sinus rhythm (right) The lower record shows Lead I ECG tracing during tachycardia while atrial pacing was being performed In the diagram below the record AP denotes the atrial pacing spike A V the atrioventricular conduction and V the onset of ventricular depolarization F signifies a fusion beat and C the onset of capture which persisted for seven beats The QRS of the captured beats is similar to that in the same lead during normal sinus rhythm The P waves are obscured by the QRS complex and the pacemaker spike R interval is 0 29 sec The rate during capture is 204 per minute the basic rate of the tachycardia 194 per minute Capture ceases when the pacemaker spike R interval prolongs and increased antegrade block occurs allowing emergence of the ventricular tachycardia

fusion beat ventricular capture occurred with a prolonged P R interval (0 29 sec) and a QRS configuration similar to that present in Lead I during normal sinus rhythm This established a diagnosis of ventricular tachycardia Conversion to sinus rhythm could not be accomplished by sustained capture followed by gradual lowering of the pacing rate The patient was then electrically cardioverted and maintained on an intravenous lidocaine infusion

Subsequently a Holter Recorder 10 hour monitoring of his ECG revealed numerous short runs of ventricular tachycardia (Fig 5) usually initiated by a ventricular premature contraction There was a constant coupling interval between the ventricular premature contraction and the onset of the tachycardia These tachycardias showed complete A V dissociation with spontaneous terminations

While hospitalized the patient continued to have frequent episodes of ventricular tachycardia and required 14 cardioversions over a five week period His treatment included numerous antiarrhythmic medications including the experimental agents bretylium disopyramide and alprenolol and trials of both atrial and ventricular transvenous pacing Because of failure of medical treatment coronary angiography and left ventricular angiography were performed to search for a lesion which might be amenable to surgical therapy He was found to have significant disease of the right and left circumflex coronary arteries and an akinetic area in the posterior wall of the left ventricle On Aug 28 1970 partial excision of the left ventricular scar and a saphenous vein bypass graft to the right coronary artery was accomplished Evidence of old pericarditis was noted at the time of operation In the six months since the operation he has had no further episodes of ventricular tachycardia Treatment with oral procainamide has been continued because of ventricular premature beats

Discussion

Classically, the diagnosis of ventricular tachycardia has rested upon the presence of a wide aberrant QRS pattern with independent atrial and ventricular activity However, it is well established that neither aberration of the QRS complex nor the presence of A V dissociation unequivocally indicates a ventricular origin of a rhythm

In a tachycardia with an aberrant QRS complex and nondetectable atrial activity in the standard ECG leads, esophageal or intra atrial lead records may demonstrate the relationship of atrial and ventricular depolarization[4] The diagnosis of an atrial tachycardia can be made with this technique by demonstrating antegrade conduction At rapid atrial rates or with a prolonged PR interval, however, distinguishing between antegrade and retrograde A V conduction can be difficult His bundle records may prove helpful in this regard[5] Retrograde activation of the atria occurs in junctional tachycardia, and the finding of an R retrograde P interval of 0 10 sec

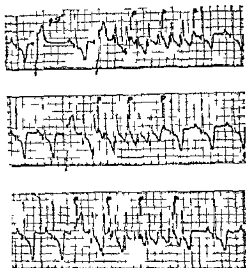


Fig 5 Three Holter Monitor recorded ECG strips demonstrating brief runs of tachycardia with a wide aberrated QRS and a rate of 194 per minute initiated in each case by a ventricular premature beat There is a constant coupling interval of 0 52 sec between the ventricular premature beat and the onset of tachycardia In contrast to the 2 1 retrograde block pattern seen during sustained tachycardia in these spontaneously terminated arrhythmias there is complete A V dissociation P denotes the P waves

ond or less proves a junctional focus [1] However junctional tachycardia may occur with retrograde block and complete and incomplete A V dissociation [6,8] Moreover ventricular tachycardia is frequently associated with retrograde V A conduction of varying degrees [9,10] Therefore when the R P interval is greater than 0 10 second or when there is A V dissociation the origin of a tachycardia may be uncertain

The presence of aberration does not distinguish a ventricular from a junctional origin Four types of aberration of supraventricular beats are known to occur[1] (1) abnormal intraventricular conduction of all conducted supraventricular beats i e bundle branch block (2) conduction through an anomalous pathway i e in the Wolff Parkinson White syndrome (3) aberration of junctional escape beats (4) rate related aberration secondary to incomplete recovery of the conducting system during conduction above a particular rate There is some question as to the mechanism of aberration which occurs in junctional escape beats [11,12] It seems likely as described by Kistin [13] that conduction via paraspecific fibers can result in aberration of junctional premature and escape beats Tachycardias originating in such fibers could conceivably occur and demonstrate fusion and capture phenomena However the degree of aberration in such beats is not great[11,13] and the QRS is generally not prolonged to greater than 0 12 second unless a coexistent aberration due to incomplete recovery is also present [13] Abnormal intraventricular conduction and the Wolff Parkinson White syndrome may be detected by examination of the ECG during normal sinus rhythm A major diagnostic problem therefore lies in determining if a rate related aberration with a junctional focus is the cause of a prolonged abnormal QRS during a recurrent tachycardia

In the patient described in this report competitive atrial pacing was used to rule out rate related aberration with junctional tachycardia by demonstrating that the conduction system was capable of transmitting impulses without aberration at a rate greater than that of the tachycardia Because of the marked degree of aberration and prolongation of the QRS in this patient s arrhythmia a junctional tachycardia with aberration due only to conduction via paraspecific fibers[13] was not considered a reasonable possibility Thus sustained atrial capture established the diagnosis of ventricular tachycardia in this case We believe that the usefulness of this technique reported previously in the case described by Lasley and Goldstein [2] deserves further emphasis In certain circumstances it may be the only way to eliminate a rate related aberration as a diagnostic possibility in a tachycardia with an abnormal QRS configuration

Another technique which deserves consideration when approaching problems of this kind is a Holter Recorder monitoring [14] Frequently the mode of onset of a tachycardia will reveal its mechanism In the case of a supraventricular tachycardia with a rate related aberration of the QRS for example the arrhythmia may begin with a P wave or the first complex of the tachycardia may not be aberrant [6] In ventricular tachycardia the arrhythmia may begin with a ventricular premature contraction

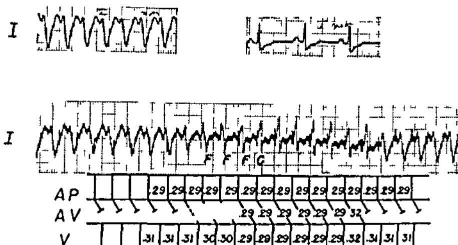


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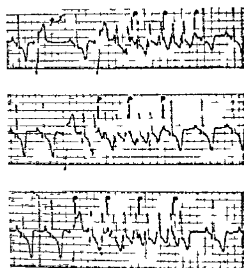


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in or near the "vulnerable" period of the T wave. The onset of a tachycardia may be very elusive. However, with the Holter Recorder, a 10 hour record is obtained, which in this case contained a surprising number of brief runs of tachycardia. The analysis of these tracings was helpful in confirming the diagnosis of ventricular tachycardia. In addition, the finding of a constant coupling interval between a ventricular premature contraction and subsequent onset of ventricular tachycardia suggests that a re-entry mechanism was involved in the genesis of the arrhythmia.

The documented history in this case of conversion of tachycardia on two occasions to normal sinus rhythm by administration of neosynephrine is interesting. The configuration of the QRS on these occasions was somewhat different from that of the patient's usual ventricular tachycardia and the rate slightly slower (Fig. 1, C). It would seem reasonable to assume that these arrhythmias were also ventricular tachycardia, in that the conduction system was subsequently shown to be capable of conducting normally at a rate greater than that of the tachycardia. The conversion to sinus rhythm of a tachycardia by a maneuver which increases the vagal tone usually indicates a supraventricular focus. In this case, carotid sinus pressure and edrophonium were ineffective in terminating the arrhythmia. Neosynephrine may have been effective by virtue of its catecholamine effect on the electrophysiologic properties of the myocardium rather than by increasing vagal tone by its blood pressure elevating effect. Conversion of the tachycardia with a vasopressor initially confused the diagnosis and is another example of the difficulties which may be encountered in distinguishing between ventricular tachycardia and junctional tachycardia with aberration.

Once the diagnosis of ventricular tachycardia was made, failure to achieve control of the arrhythmia by medication and pacing led to a study of the ventricle by means of coronary arteriography and left ventricular angiography. Han[1] has described several mechanisms whereby myocardial ischemia may cause ventricular irritability, and there have been several reports of intractable ventricular tachycardia associated with left ventricular aneurysm cured by resection of the aneurysm.[16-1] Therefore both ischemia due to the coronary artery disease and the akinetic area of the ventricular wall were considered possible etiologic factors in the development of the tachycardia, and both coronary bypass surgery and excision of a major portion of the akinetic fibrotic area were performed. The success of the operation in this case may have been due to infarctectomy, coronary artery bypass, or infarction of a small portion of the myocardium during operation.

Fortunately, tachycardias which cannot be adequately controlled medically are rare. When they are encountered, their mechanism must be accurately defined before major surgery is considered. Atrial recording, competitive atrial pacing, His bundle recordings, and Holter Recorder monitoring can aid the clinician considerably in distinguishing between ventricular tachycardia and supraventricular tachycardia with rate-related aberration of the QRS complex.

Summary

A man with a history of remote myocardial infarction developed refractory recurrent tachyarrhythmia with widened QRS complexes. Conversion to sinus rhythm during administration of intravenous vasopressors occurred on several occasions and the arrhythmia was considered to be supraventricular tachycardia with aberration of the QRS. Atrial recording, competitive atrial pacing, and Holter monitoring were used to establish a diagnosis of ventricular tachycardia. Subsequent to coronary artery bypass surgery and partial excision of a noncontractile scar from the posterior wall of the left ventricle he has had no further tachyarrhythmias. The difficulties in differential diagnosis and the techniques used are discussed.

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Double-outlet right ventricle with left ventricular-right atrial communication: Fibrous obstruction of left ventricular outlet by membranous septum and tricuspid leaflet tissue

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Severe obstruction of the left ventricular outflow tract occurs infrequently with double outlet right ventricle and is of two general types: (1) muscular, and (2) fibrous.

Muscular obstruction is produced by abnormal conal myocardium beneath the great arteries. Such musculature markedly narrows the ventricular septal defect that serves as the only outlet from the left ventricle.[1,2] Excision of this conal musculature enlarges the ventricular septal defect by raising its "roof," thereby removing the obstruction to the left ventricular outflow tract and permitting successful repair by open heart surgery.[2,3]

Fibrous obstruction of the left ventricular outflow tract is produced by endocardial cushion tissue of the atrioventricular canal, usually by tissue related to the mitral valve.[4,5] In the unique case to be presented, obstruction is produced by endocardial cushion tissue related to the tricuspid (not the mitral) valve. Fibrous obstruction of the left ventricular outflow tract associated with double outlet right ventricle has not as yet been corrected surgically.

Case report

This 35 day old white male infant weighed 4.83 kilograms at birth. The mother's pregnancy had been uncomplicated and delivery had been normal. Cyanosis, tachypnea, and splenomegaly were noted immediately after birth. Oxygen (30 per cent) reduced the cyanosis and the patient was digitalized because of cardiomegaly.

Physical examination on admission to the Fort Worth Children's Hospital when he was 15 days old revealed cyanosis of the lips and nailbeds. Weak pulses were present in all extremities and flush blood pressures (mm. Hg) were: right arm 110, left arm 100, and right leg 90. Auscultation revealed a nor-

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Fig. 1 Chest roentgenogram showing cardiomegaly (cardiothoracic ratio = 70 per cent), uptilted apex and somewhat increased pulmonary vascular markings.

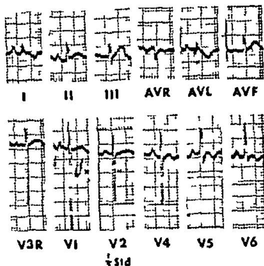


Fig. 2 Electrocardiogram suggests left ventricular hypertrophy and right atrial enlargement with mild prolongation of P R interval (0.15 sec.)

mal first heart sound, splitting of the second heart sound, a third heart sound (diastolic gallop) at the lower left sternal border and Grade 3/6 systolic and diastolic murmurs that were heard best at the apex and left axilla. The lungs were clear to auscultation. The liver was palpated 4 cm. below the right costal margin and the spleen 2 cm. below the left costal margin.

Chest roentgenograms showed progressive cardiomegaly, a globular heart with an uptilted apex and mildly increased pulmonary vascular markings (Fig. 1). Electrocardiography suggested left ventricular hypertrophy and right atrial enlargement with a somewhat prolonged P R interval of 0.15 sec. for a rate of 140 per minute (Fig. 2) top normal being 0.11 sec.[9]

Cardiac catheterization when the patient was 25 days of age demonstrated a left-to-right shunt with oxygen step-ups at the right atrial and right ventricular levels (Table I). The catheter entered a persistent left superior vena cava via the coronary sinus. The catheter also passed directly from the right atrium into the left atrium, the left atrium was never entered. The right ventricular pressure was high (90/0-5 mm. Hg) but the left ventricular pressure was 70 mm. Hg higher (160/0-10 mm. Hg). Although neither great artery was entered, the left ventricular pressure was very probably suprasystemic in view of the flush blood pressures of 90 to 110 mm. Hg noted above.

Selective right ventricular angiocardiography revealed that both great arteries arose from the right ventricle (Fig. 3). The left atrium and left ventricle were never visualized. The aortic valve was to the right, posterior and inferior relative to the pulmonary valve (Fig. 3b). A curvilinear filling defect beneath the aortic valve suggested subaortic stenosis (Fig. 3b). This suggestion was strengthened by the demonstration of moderate tubular hypoplasia of the distal aortic arch (Fig. 3b) which is consistent with a low flow aortic arch secondary to subaortic stenosis. A patent ductus arteriosus was not visualized.

Progressive intractable heart failure led to death at 35 days of age.

At necropsy, external inspection of the heart accurately suggested right ventricular hypertrophy and enlargement, the apex being formed largely by the right ventricle (Fig. 4a). Enlargement of the main pulmonary artery, mild hypoplasia of the ascending aorta and moderate hypoplasia of the aortic arch were also evident (Fig. 4a).

The interior of the right atrium revealed (Fig. 4b) marked hypertrophy and enlargement, striking hypoplasia of the right superior vena cava which admitted a 1 mm. probe snugly, a prominent Thebesian valve only partly covering a very much enlarged coronary sinus (10 mm. in diameter) which received a persistent left superior vena cava, a fossa ovalis, i.e., an anatomically sealed foramen ovale, unusual at 35 days of age, and a left ventricular-to-right atrial communication within the superior commissure of the tricuspid valve at the junction of the anterior and septal leaflets measuring 1.5 mm. in diameter and surrounded by thickened, firm tricuspid leaflet tissue. This small communication was the only outlet from the left ventricle—indeed the only outlet from the left side of the heart.

The tricuspid valve was enlarged (circumference = 5.5/3.3 cm.) (Fig. 4b) and the right ventricle was hypertrophied and enlarged (Figs. 4b-d). No ventricular septal defect could be seen from within the right ventricle (Figs. 4c, d). At first glance the aortic valve appeared to be separated from the tricuspid valve by a 3 mm. wide band of subaortic conal musculature (Fig. 4c). However, on closer inspection the anterior leaflet of the tricuspid valve appeared to be in direct fibrous continuity with the left coronary and noncoronary leaflets of the aortic valve—behind this slim band of conal musculature. Such continuity was confirmed by dividing this band of conal muscle (Fig. 4d). This band of conal musculature (Fig. 4c) was very similar morphologically to the structure designated as the right posterior division of the

Double-outlet right ventricle with left ventricular-right atrial communication: Fibrous obstruction of left ventricular outlet by membranous septum and tricuspid leaflet tissue

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Severe obstruction of the left ventricular outflow tract occurs infrequently with double outlet right ventricle and is of two general types: (1) muscular, and (2) fibrous.

Muscular obstruction is produced by abnormal conal myocardium beneath the great arteries. Such musculature markedly narrows the ventricular septal defect that serves as the only outlet from the left ventricle.[1,2] Excision of this conal musculature enlarges the ventricular septal defect by raising its "roof," thereby removing the obstruction to the left ventricular outflow tract and permitting successful repair by open heart surgery.[3]

Fibrous obstruction of the left ventricular outflow tract is produced by endocardial cushion tissue of the atrioventricular canal, usually by tissue related to the mitral valve.[4,5] In the unique case to be presented, obstruction is produced by endocardial cushion tissue related to the tricuspid (not the mitral) valve. Fibrous obstruction of the left ventricular outflow tract associated with double outlet right ventricle has not as yet been corrected surgically.

Case report

This 35 day old white male infant weighed 4.0 kilograms at birth. The mother's pregnancy had been uncomplicated and delivery had been normal. Cyanosis, tachypnea, and splenomegaly were noted immediately after birth. Oxygen (50 per cent) reduced the cyanosis and the patient was digitalized because of cardiomegaly.

Physical examination on admission to the Fort Worth Children's Hospital when he was 15 days old revealed cyanosis of the lips and nailbeds. Weak pulses were present in all extremities and flush blood pressures (mm. Hg) were: right arm, 110; left arm, 100; and right leg, 90. Auscultation revealed a nor-

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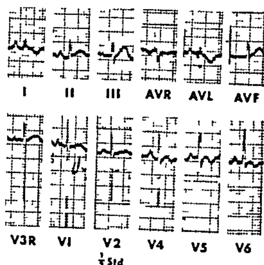


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The tricuspid valve was enlarged (circumference = 5 5/3 3 cm) (Fig 4b) and the right ventricle was hypertrophied and enlarged (Figs. 4b-d) No ventricular septal defect could be seen from within the right ventricle (Figs 4c d) At first glance the aortic valve appeared to be separated from the tricuspid valve by a 3 mm. wide band of subaortic conal musculature (Fig 4c) However on closer inspection the anterior leaflet of the tricuspid valve appeared to be in direct fibrous continuity with the left coronary and noncoronary leaflets of the aortic valve—behind this slim band of conal musculature Such continuity was confirmed by dividing this band of conal muscle (Fig 4d) This band of conal musculature (Fig 4c) was very similar morphologically to the structure designated as the right posterior division of the

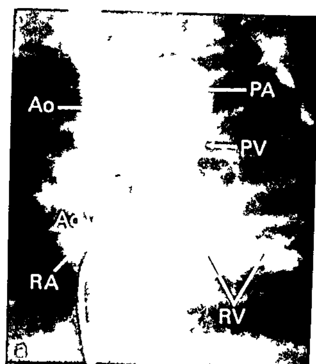


Fig. 3a. Selective right ventricular angiocardiogram. Posteroanterior projection. Aorta (Ao) and pulmonary artery (PA) both arise above morphologically right ventricle (RV). Pulmonary valve (PV) is anterior, superior, and to the left of aortic valve (Ao V). PA is dilated. RA = right atrium.

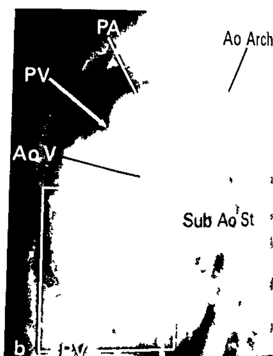


Fig. 3b. Selective right ventricular angiocardiogram. Lateral projection. A curvilinear filling defect is seen beneath aortic valve (Ao V), accurately suggesting subaortic stenosis (Sub Ao St). Transverse aortic arch (Ao Arch) displays tubular hypoplasia. PA = pulmonary artery; PV = pulmonary valve; RV = right ventricle.

Table I. Cardiac catheterization findings

Site	O_2 saturation (%)	Pressure (mm Hg)
Left superior vena cava	52	
Right atrium	57	a = 7 v = 4
Right ventricle	78	90/0-5
Left ventricle	98	160/0-10
Right ventricle → Right atrium → Left ventricle		80/0 8 → a = 10 → 160/0-10

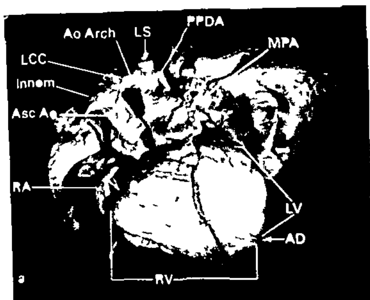
septal band in a previous study of truncus arteriosus communis (see Fig. 4a and c of that paper).[10]

Why is this structure not a hypoplastic parietal band (crista supraventricularis)? It looks quite like it—running from the ventricular septum to the parietal (free) wall above the pars membranacea septi and the anterior leaflet of the tricuspid valve (Figs. 4c, d). This conal musculature could certainly be regarded as *a* parietal band in the sense that it runs to the parietal wall. However, this structure may well not represent *the* parietal band because the structure so designated also forms the conal septum dividing the aortic and pulmonary outflow tracts. In this heart there was no conal septum dividing the aortic and pulmonary outflow tracts, i.e., there was no grossly recognizable myocardium beneath the aorticopulmonary septum, the semilunar valves being in direct fibrous continuity with each other (Fig. 4c). Hence the parietal band (crista supraventricularis) appeared to be absent, at least superiorly.

However, this band of conal musculature could represent the inferior (caudal) end of the true parietal band if a large conal septal defect were present superiorly beneath the aorticopulmonary septum (Fig. 4c).

This band of conal myocardium is not regarded as subaortic conal free wall (as distinct from conal septal) musculature because division of this band demonstrated aortic-tricuspid fibrous continuity behind it (Fig. 4d).

This conal band was visualized angiocardiographically (Fig. 3b). It appeared to produce a most uncommon type of muscular subaortic stenosis, leading to hypoplasia of the aortic arch, probably because of reduced aortic blood flow. Had this band of conal muscle not been located where it was (Figs. 4c, d), the high ventricular septal defect usually



Figs. *4a* through *4f*. Autopsy specimen of heart and lungs. *a*, External frontal view accurately suggests hypertrophy and enlargement of right ventricle (*RV*). Note that *RV* forms cardiac apex. This in turn gives a sigmoid contour to anterior descending coronary artery (*AD*). More than the usual amount of left ventricle (*LV*) is seen from the front, accurately suggesting left ventricular hypertrophy and enlargement. Right atrium (*RA*) appears hypertrophied and enlarged, but left atrium is not seen from the front. Relation between great arteries appears to be normal. Main pulmonary artery (*MPA*) is dilated. Ascending aorta (*Asc Ao*) is mildly hypoplastic, hypoplasia of transverse aortic arch (*Ao Arch*) becoming moderately marked distal to innominate artery (*Innom*). Functionally closed but probe patent ductus arteriosus (*PPDA*) is seen. *LCC* = left common carotid artery. *LS* = left subclavian artery. Photography in Figs. *4a* through *4f* was by Pauline McRae, Marilee Calendo, and Terence Wrightson; lettering was by Donna Larina.

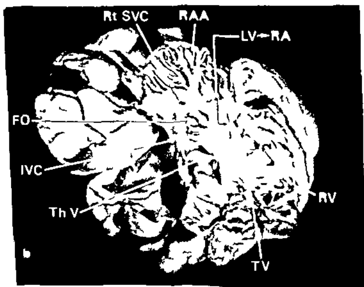


Fig. *4b*. Opened right atrium, tricuspid valve (*TV*), and right ventricular inflow tract (*RV*). Note the hypertrophy and enlargement of the right atrial appendage (*RAA*) and RA, marked hypoplasia of ostium of right superior vena cava (*Rt SVC*), sealed foramen ovale or fossa ovalis (*FO*), prominent Thebesian valve (*Th V*) partly covering the markedly enlarged ostium of coronary sinus that receives a persistent left superior vena cava, enlarged tricuspid valve (*TV*), small *LV-RA* communication opening into superior commissure of *TV* and serving as sole outlet from left side of heart.

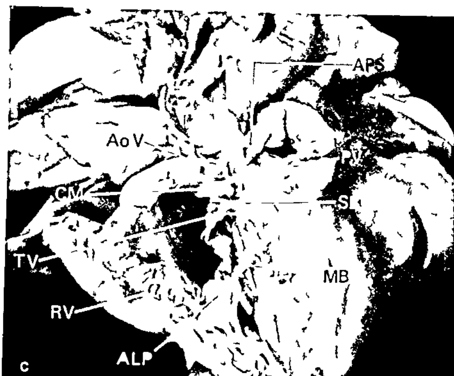


Fig 4c Right ventricular outflow tract Both great arteries arise from *RV* There is no parietal band or conal septum beneath aorticopulmonary septum (*APS*) Hence aortic valve (*Ao V*) and pulmonary valve (*PV*) are in fibrous continuity Beneath *Ao V* there is a 3 mm wide band of conal musculature (*CM*) running from ventricular septum to *RV* free wall above anterior leaflet of tricuspid valve (*TV*) *CM* probably produced subaortic stenosis (Fig 3b) *CM* is very similar morphologically to right posterior division of septal band (*SB*)[11] but could represent an inferior remnant of parietal band (conal septum or crista supraventricularis) *Ao V*-*TV* fibrous continuity appeared to be present behind (dorsal to) *CM* *ALP* = anterolateral papillary muscle *MB* = moderator band

associated with double outlet right ventricle very probably would have been present in this case Hence although it is accurate to describe the severe obstruction of the left ventricular outflow tract in this case as fibrous (produced by pars membranacea septi and by the anterior and septal leaflets of the tricuspid valve) this conal band (Fig 4c) also appears to have played an essential if secondary role by reducing the size of the interventricular foramen sufficiently for it to be obstructed by atrioventricular endocardial cushion tissue

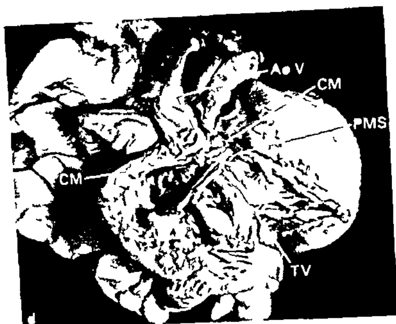
Despite the apparent subaortic stenosis produced by this band of conal myocardium the aortic valve was tricuspid and of normal size (circumference = 2 3/2 2 cm) (Fig 4c) The pulmonary valve was tricuspid and enlarged (circumference = 3 3/2 6 cm) (Fig 4c) The subpulmonary conus was not underdeveloped in the sense that the minimum distance between the pulmonary valve and the tricuspid valve was normal (7/6 mm) The coronary ostia and distributions were normal The ductus arteriosus was functionally closed but probe patent (Fig 4a) Hypoplasia of the aortic arch was moderate (circumference = 0 9/1 2 cm) (Figs 3b and 4a)

The left atrium (Fig 4e) was hypertrophied but not enlarged The mitral annulus was somewhat smaller than normal (1 9/2 5 cm) but congenital mitral stenosis did not appear to be present there being no obliteration of interchordal spaces or reduction of interpapillary muscle distance (Fig 4e) However the papillary muscles were hypoplastic (Fig 4e)

The left ventricle (Fig 4f) was hypertrophied and enlarged The fibrous obstruction of the left ventricular outflow tract could be seen with some difficulty from the left ventricular aspect (Fig 4f) but was readily apparent from the right atrium (Fig 4b) the only outlet from the left side of the heart being a small left ventricular-to-right atrial communication

Discussion

This is the first reported case of a remarkable anomaly double outlet right ventricle in which the only outlet from the left side of the heart is a small left ventricular-to-right atrial communication Severe obstruction of the left ventricular outflow tract was produced by atrioventricular endocardial cushion tissue that was intimately related to the *tricuspid valve* (Fig 4b) In this regard it should be recalled that the pars membranacea septi is formed by atrioventricular endocardial cushion tissue intimately related to the tricuspid valve (the right tubercles)[11, 12] and that a left ventricular to right atrial communication is a defect in the atrioventricular portion of the pars membranacea septi[13] Hence improbable though it may seem, it is only a



4d Division of *CM* proved *Ao V TV* fibrous continuity Note that no ventricular septal defect is visible
m within *RV* The *LV RA* defect is within pars membranacea septi (*PMS*) See also Fig 4b

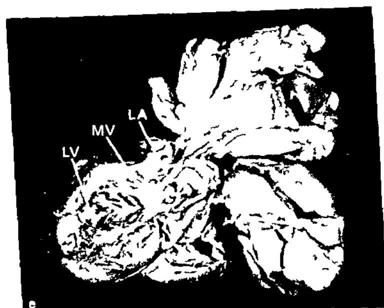


Fig 4e Opened left atrium (*LA*) mitral valve (*MV*) and left ventricle (*LV*) *LA* is hypertrophied but not enlarged *MV* is mildly hypoplastic as are associated papillary muscles *LV* is otherwise hypertrophied and enlarged

slight oversimplification to state that in this case severe stenosis of the left ventricular outflow tract was produced by tricuspid valvular tissue (Fig 4b)

Nor is this case entirely without precedent Obstruction of the left ventricular outflow tract due to atrioventricular endocardial cushion tissue related to the mitral valve has been reported[4,5] Tricuspid valvular tissue also has infrequently been documented as a cause of obstruction of the left ventricular outflow tract[13,14] but not in

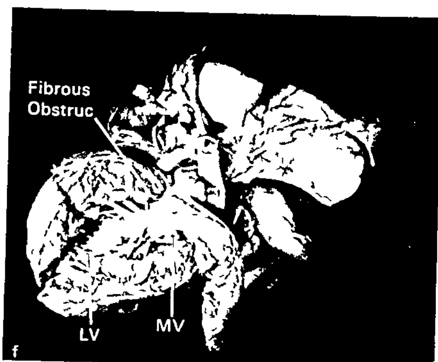


Fig 4f LV outflowtract leading to fibrous obstruction (*Fibrous Obstruc*)

association with double outlet right ventricle

It has been previously suggested[2] that obstruction of the left ventricular outflow tract be incorporated into classifications of double outlet right ventricle It is now known that such obstruction can be either muscular[1,3] or fibrous (this case) The muscular type of obstruction is amenable to correction by open heart surgery[2,3] The fibrous type has not been repaired surgically to date The anatomic findings in the present case seem to suggest that surgical correction would be difficult or impossible The interventricular portion of the pars membranacea septi is so small (5 by 2 mm) that even complete removal of the membranous part of the ventricular septum probably would not eliminate the obstruction to the left ventricular outflow tract Thus on the basis of the very limited data available, it seems probable that the muscular type of obstruction can be corrected surgically but that the fibrous type of obstruction may prove to be inoperable by present methods

Will it be possible to make the differential diagnosis between the operable muscular type of obstruction and the probably inoperable fibrous type? Data are presently far too limited to permit a definite answer to this question However, high quality angiocardiography might well make it possible to recognize the presence of a muscular subaortic conus with a somewhat higher and more anterior aortic valve in the muscular type,[2] as opposed to the absence of a subaortic conus with a relatively lower and more posterior aortic valve in the fibrous type (Fig 3)

There is a widespread view that double outlet right ventricle is characterized by semilunar valves that are approximately side by side and at about the same height,[17,18] associated with a bilateral conus (persistent bulboventricular flange)[19] The present case is an exception to all of the foregoing generalizations This case demonstrates that it is possible to have double-outlet right ventricle with a unilateral (subpulmonary) conus Absence of subaortic conal musculature is indicated by the presence of aortic tricuspid fibrous continuity (Fig 4d) A bilateral conus (persistent bulboventricular flange) is not essential to the morphogenesis of double outlet right ventricle For reasons that remain unclear, the membranous septum formed beneath the *left* side of the aortic valve in this case, instead of beneath the right side as occurs normally

Summary

Double outlet right ventricle can be

sociated with obstruction of the left ventricular outflow tract of two types muscular and fibrous The muscular form can be corrected by open heart surgery but the fibrous type may prove to be inoperable by present methods The angiocardiographic differential diagnosis of muscular and fibrous obstructions is considered briefly

A unique case of fibrous obstruction of the left ventricular outflow tract associated with double-outlet right ventricle was presented in a 35-day old white male infant The only outlet from the left side of the heart was a small left ventricular to right atrial communication This is the first reported case of atrioventricular endocardial cushion tissue closely related to the *tricuspid* valve producing fibrous obstruction of the left ventricular outflow tract in association with double-outlet right ventricle

This case also illustrates that it is possible for double outlet right ventricle to occur with aortic atrioventricular fibrous continuity A bilateral conus—persistence of the bulboventricular flange—is not a constant finding in double-outlet right ventricle

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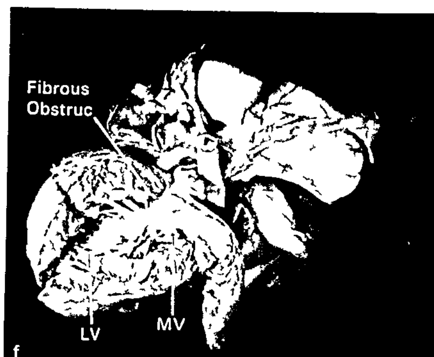


Fig 4f *LV* outflow tract leading to fibrous obstruction (*Fibrous Obstruc*)

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Summary

Double outlet right ventricle can be



l g 1 Roentgenograms of an upper (A) and a lower (B) extremity show extensive calcification that outline the entire arterial tree Note lack of osteodystrophy



Fig 2 Section of radial artery demonstrates calcific infiltration of the media (arrow) and edematous intimal thickening (Hematoxylin and eosin ×20)

Azotemic arteriopathy

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*Sandor A Friedman M D ***
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The metastatic calcification seen in chronic renal failure often involves the peripheral arteries [1] This vascular calcification is not always innocent and may lead to significant arterial insufficiency [2-5] We recently had the opportunity to observe a uremic patient with widespread arterial calcification and ischemia of several organs Careful examination of his vessels at necropsy revealed an unusual lesion which may possibly be related to azotemia

Case report

S S a 60 year old Caucasian man entered the Coney Island Hospital because of progressive dyspnea on exertion and leg edema for six months He was known to have had moderate hypertension for 20 years and mild diabetes mellitus controlled by diet Three years prior to hospitalization anemia and a blood urea nitrogen (BUN) of 26 mg per 100 ml were discovered There was no history of exposure to nephrotoxins ingestion of vitamin D dysuria or hematuria

Physical examination revealed a pale orthopneic lethargic man with asterixis The blood pressure was 160/85 mm Hg and the pulse rate was 82 per minute The neck veins were distended and rales were present at both lung bases Cardiac examination revealed a heaving apical impulse in the sixth intercostal space at the anterior axillary line and a protodiastolic gallop A smooth tender liver was palpable 6 cm below the right costal margin There was pitting edema of the feet and ankles Femoral popliteal dorsalis pedis and radial pulses were palpable bilaterally but the posterior tibial pulses were absent

The hematocrit was 31 per cent and the white blood cell count was 6 900 per cubic millimeter with a normal differential The BUN was 74 mg per 100 ml the serum creatinine was 7 4 mg per 100 ml and the fasting blood sugar was 163 mg per 100 ml Twenty four hour urine collections revealed an endogenous creatinine clearance of 5 to 6 ml per minute and protein excretion of 2 5 Gm per 24 hours The serum calcium was 8 2 to 10 6 mg per 100 ml and the phosphorus was 6 9 to 8 3 mg per 100 ml The serum albumin was 2 3 Gm per 100 ml and the globulin was 3 6 Gm per 100 ml The alkaline phosphatase was 4 3 to 5 3 Bessie Lowry units A chest roentgenogram showed cardiomegaly Nephrotomograms revealed contracted kidneys X rays of the hands failed to demonstrate subperiostial bone resorption but did show calcification of the digital arteries

The patient was treated with digoxin and furose

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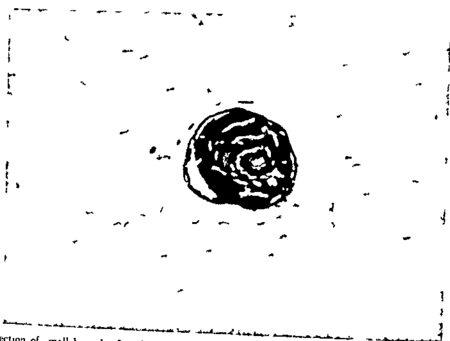


Fig 4 Section of small branch of middle cerebral artery in corpus callosum demonstrates massive calcific replacement of the media, sparing of the intima, and severe reduction in luminal caliber (Hematoxylin and eosin ×128)

eighin 2 grams Microscopic examination revealed chief cell hyperplasia with groups showing eosinophilic transformation of the cytoplasm No fat cells were seen Multiple sections of bone were grossly and microscopically normal No evidence of increased resorption was seen

Discussion

Arterial calcification even without other evidence of metastatic deposits is not uncommon in patients with chronic renal failure[1,3,6,7] Although the arterial involvement can be clearly visualized by plain roentgenography there usually is no obvious clinically significant vascular impairment However several patients have been described with serious problems attributable to this calcific process Mallick and Berlyne[2] described three uremic patients taking vitamin D who developed massive calcium deposition that prevented insertion of shunts for hemodialysis In addition there have been three reports of calcific arterial occlusion and digital gangrene in uremic patients[4,5]

The present case of widespread arterial calcification and gangrene of the upper and lower extremities in association with uremia is the first to be reported with complete histology which seems to point to the reason for the arterial insufficiency Arterial pathology and obstruction of an extraordinary nature and extent was found not only in the vessels of the extremities but also in the blood supply of the brain and entire gastrointestinal tract The histologic appearance of the arteries demonstrated marked luminal compression due mainly to heavy calcific infiltration of the media and partially to reactive connective tissue swelling and hyperplasia of the intima (see Figs 2 to 4) This pathology is clearly different from arteriosclerosis obliterans seen in patients with diabetes mellitus where arterial obstruction is associated with atheromatous replacement of the intima

Although medial calcification also occurs in medium sized arteries in many non uremic individuals (Monckeberg sclerosis) in such instances it does not result in arterial obstruction A vasculitis or collagen disease is excluded as the cause of arterial insufficiency in our patient by the absence of thrombosis and inflammatory reaction

The pathogenesis of arterial calcification in uremia is not well understood but must be related to altered calcium metabolism Renal failure results in acidosis increased



Fig 3 Section of submucosal branch of the gastric artery shows marked medial calcification (Hematoxylin and eosin ×32)

mide responded with subjective improvement and loss of peripheral edema and was discharged from the hospital During the next six months he developed progressive edema in spite of increasing doses of furosemide up to 1 5 Gm daily he became increasingly lethargic disoriented and anorectic and required rehospitalization The blood pressure was 100/70 mm Hg Again the neck veins were markedly distended and bibasilar râles were present A pleural friction rub was audible over the left lateral lung fields but cardiac findings were unchanged Anasarca with ascites and edema to the hips was present The subclavian axillary femoral popliteal dorsalis pedis and right brachial pulses were of normal intensity The right radial pulse was diminished the left brachial and radial and both posterior tibial pulses were absent The arteries had a rocklike consistency with nodular irregularities The fingers of both hands were cold and cyanotic and there was mottling and ecchymosis of the second third and fourth fingers of the left hand The right heel was frankly gangrenous

Results of blood chemistry tests were essentially unchanged except for the BUN which had risen to 182 mg per 100 and the serum creatinine which was now 9 4 mg per 100 ml X rays of all extremities (Fig 1) revealed extensive calcification of large and small arteries including the digital arteries of the hands and feet and outlining the entire arterial tree Abdominal films showed calcification of the mesenteric and iliac vessels Peritoneal dialysis was performed with good exchanges and reduction of serum creatinine to 4 1 mg per 100 ml but the patient s mental status did not improve During the next 12 days extensive gangrene of the fingers of both hands and the glans penis developed His condition progressively deteriorated and he died

Postmortem examination Necropsy revealed extensive dry gangrene of the second third fourth and fifth digits of the right hand the second third and fourth digits of the left hand the right heel and the penis

Patchy but massive calcification of the media was found in all the peripheral arteries from the iliac and subclavian to the digital vessels (Fig 2) celiac and mesenteric arteries submucosal vessels of the entire gastrointestinal tract (Fig 3) and cerebral vessels particularly the middle cerebral arteries and their branches (Fig 4) The lumina of these vessels were compressed and reduced to about one third of their normal caliber in many areas The intima was thickened in some areas by loose edematous connective tissue but was relatively free of atheromatous degeneration (Fig 2) On the other hand there was extensive partially calcified intimal atheromatosis of the renal and coronary arteries

The heart weighed 550 grams with gross dilatation and hypertrophy of both ventricles Numerous foci of fibrosis and calcification were present in the left ventricular myocardium and interventricular septum Examination of the lungs revealed calcium deposits in many alveolar septa and subpleural zones

The kidneys were atrophic weighing 180 grams together and demonstrated marked nephrosclerosis There were numerous areas of focal fibrosis and calcific deposits in the cells and lumina of the tubules (Fig 5) as well as the glomeruli

The rectal mucosa was sloughed and necrotic but the remainder of the gastrointestinal tract was intact Liver gallbladder and spleen were normal Focal fibrosis of the islets was found in the pancreas

All four parathyroid glands were uniformly enlarged to three to five times normal the largest

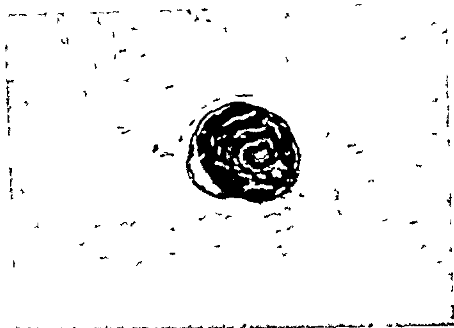


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Discussion

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dramatic event—the development of gangrene—occurred In retrospect the impairment of sensorium was out of proportion to the degree of uremia and did not improve preterminally despite adequate peritoneal dialysis Local ischemia may have been partially responsible The necrotic bowel found at necropsy was probably related to arterial insufficiency and cardiac failure

It is tempting to speculate that progressive calcific circulatory insufficiency leading to malfunction of vital organs goes undetected in some uremic patients Indeed the kidney dysfunction itself may be aggravated by a decreasing renal blood flow in some cases More data are needed to test the validity of this speculation Patients with chronic renal insufficiency should be followed with x rays taken with the proper technique for demonstrating vascular calcification and close attention should be given to the peripheral pulses Autopsies should include careful examination of the entire arterial tree

Summary

A patient being treated for chronic renal failure developed massive generalized arterial calcification with obliteration of peripheral pulses and extensive cutaneous gangrene Careful postmortem examination of his arterial tree revealed a lesion that may be related to uremia There was widespread calcific infiltration of the media of large and small arteries along with intimal swelling Arterial occlusions occurred without evidence of significant atherosclerosis or thrombosis The vascular insufficiency resulting from this lesion may have been instrumental in multiorgan failure

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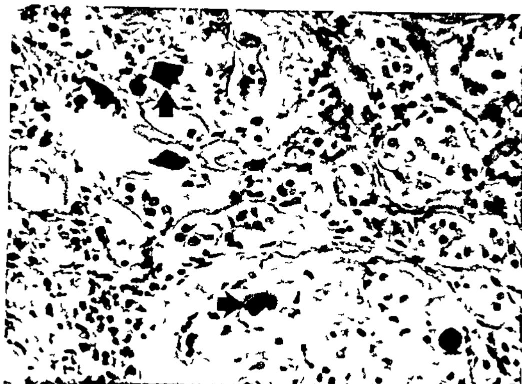


Fig 5 Section of kidney shows diffuse tubular (↑) and glomerular calcification (→) (Hematoxylin and eosin ×50)

parathyroid activity hypoproteinemia and elevated serum phosphate levels—factors which alter calcium homeostasis Chronic acidosis might lead to demineralization of bone with release of calcium into the blood and subsequent deposition in vessel walls, but this effect may be offset by the increased solubility of calcium salts in a more acidic blood

In long standing renal failure parathyroid gland hyperplasia is very common but obvious vessel calcification is seen much less often In a survey of 20 patients maintained with chronic hemodialysis arterial calcification was found in only eight of 15 patients with evidence of active hyperparathyroidism (persistent elevation of the serum alkaline phosphatase concentration)[3] Furthermore Katz and associates[8] have reported very little change in vascular calcification in four patients after parathyroidectomy despite impressive resorption of other metastatic deposits On the other hand, Massry and colleagues[4] reported a patient who developed vessel calcification and digital gangrene following renal transplantation and demonstrated first clinical and, later, radiologic improvement after subtotal parathyroidectomy

Our patient did not show radiologic or histologic evidence of osteodystrophy and had only minimal elevation of the serum alkaline phosphatase concentration However in the presence of hypoproteinemia a serum calcium level as high as 10 6 mg per 100 ml suggests that the ionized calcium level may have been slightly elevated Patients with primary hyperparathyroidism only rarely develop extensive arterial calcification despite much higher calcium levels than those seen in secondary hyperparathyroidism[9] This difference may be related to the serum phosphate concentration which is decreased in primary and elevated in secondary hyperparathyroidism It is logical to presume that the resulting high molar product of calcium and phosphate in uremia might exceed the solubility product of calcium phosphate favoring its precipitation in soft tissues If the phosphate concentration is a determining factor in this calcific process then its level should be carefully monitored and excess levels reduced by administration of aluminum hydroxide gels or by dialysis Studies are in progress to evaluate this point

In our patient the clinical significance of calcific involvement of the arterial circulation did not become apparent until a

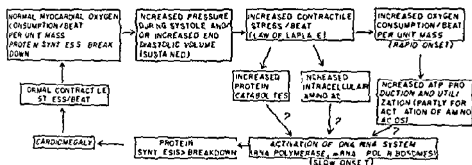


Fig. 1 Scheme illustrating the development of cardiomegaly as a negative feedback mechanism to restore myocardial energy expenditure per beat under circumstances that cause a *sustained* increase. The structural adaptation serves to prevent early failure of the myocardium.

above in brief I favor the first of the above mentioned alternatives although admittedly the supporting evidence is somewhat circumstantial

With these introductory remarks as a background we might consider the most likely pathophysiologic mechanism underlying the development of hypertrophy in a certain number of cases of coronary artery disease and/or myocardial infarction associated with long term survival. Obviously other causes of cardiac hypertrophy including hypertension which favors the development of coronary atherosclerosis are excluded from consideration

Incidence of hypertrophy

The incidence of cardiac hypertrophy in coronary atherosclerosis and myocardial infarction (in the absence of hypertension and other causes of hypertrophy) has been the subject of some controversy. In some studies the absence of arterial hypertension has been in doubt because with the onset of infarction blood pressure can fall to normal levels and may never regain its original values. Other studies have been based on roentgenologic examination of the cardiac shadow without the use of contrast media.[37, 40] Such reports must be excluded since dilatation and hypertrophy cannot be distinguished by this means. Postmortem studies are essential and the absolute heart weight or better the heart weight to body weight ratio and microscopic measurements of fiber diameter are still the best available means for assessing the existence of myocardial hypertrophy (provided that cellular hydration or edema is ruled out or accounted for). A further consideration is the number of cases reported in a given study. Older literature has been particularly prone to draw conclusions on the basis of a small number of cases examined

Gross and associates[41] reviewed the necropsy reports of 8,500 cases from several hospitals and sorted out those with coronary atherosclerosis and myocardial infarction in the absence of hypertension nephrosclerosis and diabetes. Analysis of the data led them to the conclusion that myocardial infarction is probably not causally related to cardiac hypertrophy. Miller and Weiss[42] studied 19 cases of advanced coronary disease with scattered areas of fibrosis and various degrees of multiple infarction and found none to have cardiac hypertrophy on the basis of the absolute heart weight. They emphasized the view that indisputable and advanced coronary disease need not lead to gross cardiac hypertrophy. Bell and Clawson[43] studied hypertensive heart disease and maintained that coronary disease by itself did not cause cardiac hypertrophy. Other observers were unable to find a relationship between myocardial fibrosis due to coronary disease and cardiac hypertrophy.[44, 45] In contrast to these studies many investigators have reported the occurrence of cardiac hypertrophy (findings based on postmortem observations) in a certain percentage of patients with marked coronary atherosclerosis with or without infarction who had no evidence of chronic hypertension or other diseases that would have caused hypertrophy of the heart.[46]

Current opinion favors the view that a

Review

Pathogenesis of cardiac hypertrophy in coronary atherosclerosis and myocardial infarction

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The problem of the pathogenesis of cardiac hypertrophy like most others may be likened to a jigsaw puzzle The solution of such a puzzle tends to be more difficult at the start and gets easier toward the end when the parts begin to fit together in rapid succession It may be fair to state that in recent years the numerous components of the puzzle of cardiac hypertrophy seem to be falling rapidly into their proper places to complete the picture The pathogenetic sequence of events leading to myocardial hypertrophy is now understood better than ever before I have schematically outlined this in a recent Symposium on Hypertrophy of Heart Muscle[1] A modified version of the scheme is presented in Fig 1 Hypertrophy is regarded as a negative feedback mechanism to restore to normal the *energy expenditure of a unit mass of muscle per beat* whenever there is a *sustained* increase in stroke energy expenditure per unit mass of myocardium[2,3] The functional value of this structural adaptation is to prevent the early failure of the heart in chronic conditions which tend to exhaust the energy reserves of the myocardium Current thinking has brought to focus the importance of increased mean contractile 'stress' (or tension) developed per beat as a major (but not the sole) determinant of stroke energy expenditure of the myocardium[4-13] There is a host of pathologic conditions, both intrinsic and extrinsic to the heart, that might bring about such a sustained increase in contractile stress of the myocardium During the last decade considerable progress has been made at the biochemical level in understanding the molecular events which accelerate myocardial protein synthesis during the development of hypertrophy[14-] However, it is still uncertain what the exact mechanism is for causing an increase in myocardial protein synthesis The following views have been proposed without convincing experimental evidence in favor of any one of them (1) Increased production and utilization of energy rich phosphates (ATP CP) stimulate protein synthesis probably by "activating the amino acids and nucleotides[3,33] (2) Increased breakdown of cardiac proteins produces macromolecules which may inactivate repressors synthesized by a regulating gene and thereby activate the synthesis of mRNA and myocardial proteins[34] (3) Increased myocardial intracellular amino acid pool stimulates protein synthesis[35] (4) Decreased myocardial intracellular Po_2 may somehow stimulate protein synthesis[36] The arguments for or against each of these views have been discussed by me in the paper presented at the Symposium referred to

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ease requires an understanding of the many variables which may play a part in the evolution of the vascular and myocardial pathology (1) Variability in the anatomy of the coronary arteries in man both in size and in pattern is frequent[6] (2) Coronary atherosclerosis is rarely limited to one artery More often than not it is distributed over a number of vessels Thus the location with respect to the size of the vessels and the number of diseased vessels will influence the clinical and pathologic course of events (3) The enlargement of anastomotic vessels during the progressive narrowing of the affected vessels plays a very important part in the evolution of the disease The degree of narrowing of the arteries and the rapidity with which the occlusion progresses will have a profound effect on the establishment of collateral circulation and on the coronary capillary flow to the area supplied by the collateral vessels (4) The possible involvement of the collateral vessels themselves in the atheromatous process must also be taken into account

Pathologists believe that severe coronary atherosclerosis with narrowing but without complete occlusion of the lumen may cause focal or disseminated destruction of muscle tissue with fibrosis This is presumably due to localized ischemia but there is no direct evidence to support this contention Overall coronary flow by the N_2O method is normal in subjects with coronary artery disease under resting conditions[63, 64] Such patients have also exhibited normal increases in coronary flow during exercise or during administration of isoproterenol or epinephrine[6, 67] Unfortunately reliable methods are not available at the present time for the detection of diminished blood flow in *localized* areas of the myocardium in the closed chest animal or man[68] In other instances prolonged coronary insufficiency without occlusion may cause localized or extensive subendocardial necrosis of the left ventricle and papillary muscles Lesions of the papillaries are known to [illegible] in other cases[69] which would play a role in the development of hypertrophy of the left ventricle According to some the subendocardial localization of lesions in such cases is the result of normally poor circulation to these regions due to the high intramyocardial pressure and extravascular compression[70, 71] Kirk and Honig[2] and Moss[72] have shown that a low myocardial P_{O_2} prevails in these regions as compared with epicardial Whether this is or is not due to a relatively poor circulation or to a higher metabolic rate or to both remains uncertain According to Sonnenblick[74] the endocardial layers of the left ventricle should, theoretically at least have a greater O_2 consumption than the epicardial layers

There is considerable clinical evidence to suggest that chronic myocardial ischemia resulting from coronary atherosclerosis or from anomalous origin of the left coronary artery from the pulmonary artery causes cardiac dilatation In anomalous origin of the left coronary artery there is hypoxemia of the perfusing blood in addition to ischemia of the left ventricle due to low perfusion pressure In many cases the anastomotic channels between the right and the left coronary arteries are enlarged and blood flows from the aorta (high pressure) through the right coronary to the left coronary and retrograde into the pulmonary artery (low pressure)[75] In these cases the left ventricle is markedly dilated and hypertrophic with areas of fibrosis and endocardial fibroelastosis[76, 78]

The exact mechanism of cardiac dilatation in *chronic* myocardial ischemia is not clear One possibility is that chronic myocardial ischemia or hypoxia in localized areas increases the diastolic compliance of the cardiac chamber Reliable data on this important problem are not available It is more likely that coronary atherosclerosis with myocardial fibrosis causes ventricular dilatation by inducing a low grade failure of contractile function of the ventricle Nakhjavan and co workers[50] have demonstrated depressed contractility in isolated muscles from chronically ischemic myocardium of dogs whose coronary arteries were gradually constricted with Ameroid Whatever the intimate mechanism for the dilatation is it is well known that dilatation increases the contractile stress (tension) of the myocardium per beat in accordance with the law of Laplace for a given intraventricular pressure[5, 81, 82] This would lead to increased stroke energy expenditure per unit mass of heart muscle and cardiac

certain proportion of patients with marked atherosclerosis and/or myocardial infarction develops cardiac hypertrophy in the absence of hypertension or other conditions that cause cardiac hypertrophy. According to Friedberg,[55] cardiac enlargement or hypertrophy occurs in at least two thirds of the patients who survive myocardial infarction due to coronary occlusion. This relatively high incidence includes subjects with hypertensive coronary disease. Investigators who have excluded hypertensive coronary disease in their studies find a lower incidence of cardiac hypertrophy in subjects who have primary atherosclerosis of the coronaries. At present, no reliable figure may be quoted to indicate the incidence of hypertrophy in primary coronary disease.

Pathogenesis

The question is posed: What is the pathogenesis of hypertrophy in these cases? Unfortunately, experimental studies to answer this question have been remarkably few. The cardiodynamic and physiologic parameters that have to be measured during the development of hypertrophy after experimental coronary occlusion are many and varied. Fundamental studies on cardiac dynamics and metabolism are difficult to perform over a period of time in animals with chronic conditions. Thus we are left with a paucity of basic data from which to draw firm conclusions about the pathogenesis.

Experimental studies

Smith,[56] in 1918, ligated the left anterior descending coronary artery in a few dogs and reported right ventricular hypertrophy on postmortem examination. On the other hand, Sutton and Davis[57] ligated the anterior descending coronary artery in 5 dogs and exercised the animals on a treadmill postoperatively for periods varying from 23 to 319 days; no evidence of enlargement of the heart was found by plain x-ray examination (heart weights were not reported). The authors concluded that infarction per se does not cause cardiac hypertrophy. It should be noted that this type of radiologic evidence for or against hypertrophy is at best unsatisfactory. Whether exercise did or did not play any role in preventing the enlargement of the heart under these experimental conditions must also be taken into account. Katz and associates[58] induced atherosclerosis in rabbits by feeding cholesterol to them; the atheromatous process in these animals involved the coronary arteries as well as other vessels. The authors observed cardiac hypertrophy in a large proportion of the experimental animals as compared with controls. Microscopic studies of the myocardium revealed narrowing of the coronary arteries and areas of recent, organizing, and old infarcts. There was no hypertension or valvular disease and no evidence of myocarditis. The conclusion was that atherosclerosis of the coronary arteries per se can cause cardiomegaly in rabbits. However, no data were obtained to elucidate the mechanism of cardiac hypertrophy. More recently, Norman and Coers[59] ligated the anterior descending coronary arteries in rats, and reported a significant increase in the weight of the heart 6 weeks or 12 weeks after operation as compared with sham-operated animals. Almost all coronary-ligated animals demonstrated varying degrees of grossly visible infarcts. Gudbjarnason and co-workers[60] produced cardiac hypertrophy in dogs by placing Ameroid* constrictors around three coronary arteries in each experimental animal: right coronary at its origin, circumflex branch of the left coronary, and anterior descending coronary (distal to septal branch). After 7 days there was a significant increase in the weight of the left ventricle, the right ventricle, and the interventricular septum, which was not ischemic.

If myocardial infarction leads to a ventricular aneurysm, there is a tendency of the noninfarcted myocardium in that ventricle to undergo hypertrophy. Tyson and co-workers[61] showed that in dogs the establishment of a left ventricular aneurysmal sac made of fresh homologous aortic arch (which is expansile) caused hypertrophy of the left ventricle within 3 to 7 weeks. If the sac was made of Teflon, which is nonexpansile, the left ventricle did not hypertrophy.

Clinical observations

A discussion of the pathogenesis of myocardial hypertrophy in coronary artery dis-

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muscle tends to be restored to or toward normal[84] and further growth of muscle ceases. It is assumed that during the development of myocardial hypertrophy the coronary vascular system in the nonischemic regions is capable of undergoing dilatation and growth which is somewhat commensurate with the growth of the muscle. If the coronary vascular tree is incapable of such growth because of intrinsic disease, quite conceivably the hypertrophy of the heart muscle may be curtailed or prevented entirely. If this concept is true, one may explain at least partly why cardiac hypertrophy in coronary atherosclerosis is not so frequent as might be expected. Some clinical data, however, seem to support this concept. For instance, Jones[102] observed that in hypertensive patients cardiac hypertrophy was least pronounced when there was accompanying severe coronary atherosclerosis. A similar view was expressed by Bell and Clawson.[43]

The interesting observations of Gudbjarnason and associates[69] who noted myocardial hypertrophy in diffusely ischemic ventricles (induced by Ameroid constrictors) as well as in the nonischemic septum of the dog heart are difficult to explain. In these studies data such as heart rate, end-diastolic volume, left ventricular coronary flow, and oxygen consumption were lacking. The possibility of damage and edema in the ischemic areas was not ruled out.

As was pointed out earlier, many variables are involved in the development of myocardial hypertrophy in disease of the coronary arteries. This fact may explain why many patients do not develop cardiac hypertrophy. Such patients are generally those who do not exhibit congestive failure or cardiac dyssynergy prior to death from the disease. Furthermore, the failure to find an increase in the total mass of a cardiac chamber in advanced coronary disease may be partly due to the fact of replacement of muscle tissue by fibrous tissue (decreased total mass of muscle by scarring), especially when there are multiple healed infarcts with thinning of the ventricular wall. This may account for the lack of hypertrophy, as judged from the absolute weight of the heart, in some cases.

Summary

The pathogenesis of cardiac hypertrophy is now understood better than ever before. Hypertrophy is initiated either by a sustained increase in mean contractile stress (or tension) or, more likely, by a sustained increase in stroke energy expenditure of a unit mass of heart muscle. Myocardial hypertrophy occurs in a certain percentage of patients with coronary atherosclerosis and/or myocardial infarction in the absence of arterial hypertension or other diseases which cause cardiac hypertrophy. The pathogenesis under these circumstances seems to be causally related to dyssynergy and dilatation of the cardiac chamber. These changes may be caused by chronic localized ischemia of the myocardium with diffuse fibrosis (without complete occlusion) or by congestive failure arising from acute infarction and necrosis. Dyssynergy and dilatation of a cardiac chamber increase the mean contractile stress per beat and the stroke energy expenditure of the *nonischemic myocardium* which subsequently undergoes hypertrophy. It has been postulated that the regions which hypertrophy must be capable of undergoing the vascular enlargement that accompanies hypertrophy of cardiac muscle and that vascular disease may curtail this. In many cases of coronary atherosclerosis and infarction the changes described may not occur and hypertrophy will not develop if other causative factors of hypertrophy (e.g., hypertension) are absent.

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hypertrophy would ensue. It is reasonable to expect that in advanced coronary atherosclerosis the *increase in myocardial energy expenditure and hypertrophy is confined to areas of muscle which are well perfused with blood and are capable of undergoing the vascular changes* that occur with the onset of myocardial hypertrophy. The vascular changes have been extensively studied in cardiac hypertrophy induced by various means. I have reviewed this problem recently.[84] Presumably, the vascular dilatation and growth that occur in cardiac hypertrophy are associated with the increased metabolic rate of the myocardium during the period of adaptive growth of the muscle. The development of hypertrophy does not necessarily ensure that the contractile function and energetics of the cardiac chamber are completely restored to normal, particularly when the coronary arteries are narrowed. Despite the hypertrophy, there may be signs of low grade failure which would tend to further dilate the heart and aggravate the situation in the form of a positive feedback mechanism.

When acute infarction supervenes on an atherosclerotic coronary arterial tree, an *acute* cardiac failure may or may not develop depending upon the size and the location of the infarct. The latter may cause A V block, bundle branch block, papillary muscle dysfunction, mitral regurgitation, etc. In the presence of acute failure, the end diastolic volume of the heart is increased and the heart is dilated.[85] There is reduction in stroke volume and cardiac output. Tachycardia may prevail.[86-88] Tennant and Wiggers[89] and others[90,91] have shown that the acutely infarcted muscle stops contracting soon after coronary ligation and bulges out during systole. This has been described as dyssynergy of ventricular contraction by Langley and co workers[92] or asynergy of contraction by others.[93-95] The *passive* stretch of the noncontracting infarcted muscle requires that the well perfused regions of the muscle shorten to a greater extent than normal in order to raise the ventricular pressure sufficiently to open the semilunar valves and eject blood. Hood and Whiting[96] have calculated the degree of shortening of noninfarcted fibers in dogs 1 to 7 days after ligating the coronary artery and reported an increased shortening as compared with that of sham-operated dogs. Nakano[97] and West[98] have shown, with the strain gauge arch, that the contractile force of the well perfused regions of the myocardium is augmented. Langley and co workers[92] refer to this effort of the heart as "wasted internal work," a concept that is in accord with modern views of the total work of the contractile elements of heart muscle.[15,99-101] As a consequence, there will be an increase in the energy expenditure per beat of the "contractile elements" in the well perfused regions of the affected chamber. This metabolic change is believed to lead to hypertrophy of the noninfarcted muscle of the chamber. Gudbjarnason and associates[60] ligated several branches of the left coronary artery in dogs and noted an increase in protein synthesis in the *noninfarcted* regions of the left ventricle during a period of 10 days that was studied after infarction. The observations of Busch[51] lend further support to this concept. He observed that in massive infarctions of the left ventricle there was marked hypertrophy of the perfused myocardium in the free wall of the left ventricle. He described this compensatory growth as a vicarious hypertrophy. Hypertrophy will be pronounced if the infarcted area is large or is in a critical part of the myocardium that causes other functional disturbances such as papillary muscle dysfunction with mitral regurgitation, etc. If an aneurysm develops in the area of infarction it will likewise augment the energy expenditure of the muscle fibers in the well perfused regions of the heart.

If there is sufficient damage to ventricular muscle tissue, or if there is a persistent functional disturbance (e.g., papillary dysfunction), there may be clinical signs of chronic congestive failure with dilatation of the heart. These cases show the most pronounced hypertrophy on postmortem examination. Most investigators agree that chronic congestive failure is an important precursor of cardiac hypertrophy in cases of myocardial infarction or severe coronary atherosclerosis.[47, 2, 5]

When cardiac hypertrophy attains a certain level, the aerobic energy expenditure (oxygen consumption) per unit mass of

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Fundamentals of clinical cardiology

Functional diastolic murmurs

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Diastolic murmurs not caused by valve lesions and thus termed functional have been described for a long time Probably the first to be described was the Austin Flint low frequency apical rumble of aortic insufficiency[1] This was followed by the Graham Steell a high frequency basal blowing murmur caused by pulmonary hypertension in mitral stenosis[2] and by the midprecordial or apical Carey Coombs murmur of acute rheumatic fever[3] Since then functional diastolic rumbles have been described in pericardial and hypertensive heart diseases[4] acute rheumatic fever without mitral stenosis[7] and myocarditis[8] Subsequently phonocardiographic studies documented such murmurs in rheumatic coronary hypertensive and congenital heart diseases[8-11] In particular certain diastolic phenomena of mitral insufficiency[12-16] (occasional opening snap frequent third sound and nearly as frequent middiastolic rumble) have a special importance because of possible misdiagnosis of double mitral defect It is of interest that occasional diastolic murmurs (of both low and high frequency) can be found in graphic tracings of normal individuals even though such murmurs are not common on auscultation[24 25]

In spite of repeated statements and publications on this subject including several from our group[17 2-] teaching in several medical schools still persists in stating that all apical diastolic rumbles are caused by mitral stenosis thus perpetuating an erroneous concept

For this reason we shall present a few tracings obtained in a variety of conditions in order to re emphasize the frequent occurrence of apical diastolic murmurs in patients without mitral stenosis Among them the most important because they are the most misleading are those in patients with rheumatic carditis mitral insufficiency myocarditis or cardiomyopathy pulmonary heart disease or coronary heart disease

Case reports

Case 1 This patient was a 16-year old boy examined six months after the onset of the first attack of rheumatic fever At the time of recording there was no fever or joint involvement but the patient was weak the heart rate was rapid the sedimentation rate was high and the C reactive protein titer was still elevated The electrocardiogram (ECG) showed a P R interval lasting 0 20 sec. (slightly prolonged for the age) Heart rate was 100 beats per minute and blood pressure was 1?5/60 The heart was enlarged and both a systolic and a diastolic murmur were prominent There was a Grade 2 blowing systolic aortic murmur and an apical diastolic presystolic murmur

The phonocardiogram (Fig 1) showed a diamond shaped systolic murmur and a middiastolic rumble

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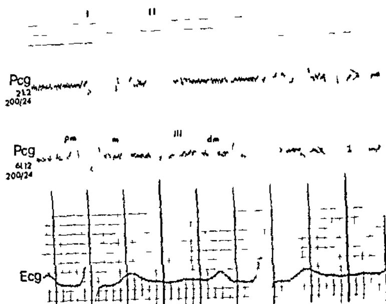


Fig. 3 Case 3—Austin Flint murmur in a 49 year old man with rheumatic aortic insufficiency. I II III = heart sounds. sm = systolic murmur. dm = middiastolic murmur. pm = presystolic murmur. The upper tracing at the second left shows better the early-diastolic murmur of aortic insufficiency. The middle tracing at the apex shows best the functional diastolic murmur.

tion showed the typical mitral systolic and aortic diastolic murmurs. When recorded without filtration (Fig. 4) the blowing murmurs were not recorded but one could see a large summation gallop sound of long duration. It was concluded that there was insufficiency of the mitral and aortic valves but no mitral stenosis. Cardiac catheterization subsequently performed excluded mitral stenosis.

Case 5. This patient was a 10-year old Negro boy with sickle cell anemia who came to observation during a crisis with loud systolic and diastolic presystolic murmurs. The heart was severely enlarged. The question of sickle cell anemia associated with rheumatic heart disease was raised.

The laboratory data excluded active rheumatic fever. The ECG was within normal limits.

The phonocardiogram was simultaneously recorded at the base and apex. In both tracings (Fig. 5) there was a diamond shaped systolic murmur. The second sound was prolonged at the base by an early-diastolic murmur that then continued with less amplitude throughout diastole and had a larger phase in presystole. A larger vibration at the apex was probably a high frequency third sound.

On the basis of the phonocardiographic findings rheumatic heart disease was excluded because the murmurs were nontypical and were extremely diffuse. Six months later a new tracing was recorded when the anemia was moderate (Fig. 5); it showed only a minimal flow murmur in systole and minimal vibrations in diastole. Thus the previous diagnosis was confirmed.

Case 6. This was a 59-year old man with a history of hypertension and evidence of minimal heart



Fig. 4. Case 4—Low frequency prolonged diastolic sound (summation gallop) giving the auscultatory impression of a middiastolic rumble in a 26-year old woman with mitral and aortic insufficiency. The apical tracing recorded without filtration, shows the complex vibration in diastole. Grade 1 A V block causes the summation of two diastolic sounds.

failure. The heart was enlarged to both the right and left but the right side was especially dilated. The pulmonary artery and its branches were very large on x-ray and the pulmonary vasculature was engorged. On auscultation there was a crescendo-decrescendo systolic murmur at the base, a loud and split second sound, and a diastolic presystolic murmur. The ECG showed biventricular hypertrophy and a Grade 1 A V block (P R = 0.32 sec.). The blood pressure was 180/110.

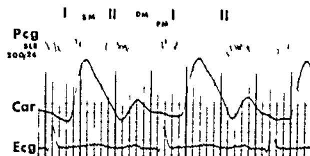


Fig. 1. Case 1. Rheumatic carditis in a 16 year old boy. *SM* = systolic murmur; *DM* = diastolic murmur continuing in presystole (*PM*). I = first sound; II = second sound; *Car* = carotid pulse tracing; *ECG* = electrocardiogram.

of high voltage continuing in presystole. One should note that the diastolic murmur started late in diastole, had a crescendo-decrescendo appearance, and then continued with a smaller presystolic phase that was not in crescendo. A high frequency tracing at the base revealed a small decrescendo early diastolic murmur of small voltage.

Cardiac catheterization was not performed because of the acute condition of the patient.

Here the diagnostic problem was whether there was a functional diastolic murmur or the rumble of mitral stenosis. The latter might have been caused by a previous unrecognized attack of rheumatic fever. The absence of an opening snap and the high voltage, high frequency, late onset, and configuration of the diastolic murmur allowed us to exclude mitral stenosis. The diastolic murmur, moreover, was out of proportion with the minimal aortic insufficiency and was not called an Austin Flint murmur.

The conclusion was: active rheumatic carditis, functional murmurs related to dilatation of the cardiac chambers. Such a conclusion was proved by the subsequent course of the patient as well as the unanimous opinion of several consultants.

Case 2. This patient was a 12 year old girl with acute rheumatic fever of two weeks' duration. The general description of the disease is similar to that of the previous case. The elevated antistreptolysin O titer and C-reactive protein confirmed the diagnosis of acute rheumatic fever. The ECG revealed a Grade 1 A-V block. On x-ray there was generalized enlargement of the heart, and the pulmonary artery was also dilated. On auscultation there was a Grade 2/6 pansystolic murmur and a Grade 3/6 low pitched diastolic rumble over the midprecordium. There were also a Grade 2 ejection systolic murmur and a Grade 2 blowing early diastolic murmur along the left sternal border.

At the apex, the phonocardiogram (Fig. 2) showed an early and midsystolic murmur. In diastole there was a pandiastolic murmur including the presystolic phase. With high frequency filtration, a small early diastolic blowing murmur was recorded at the left sternal border.

Cardiac catheterization was not performed on account of the acute condition of the patient.

The configuration and high voltage of the diastolic

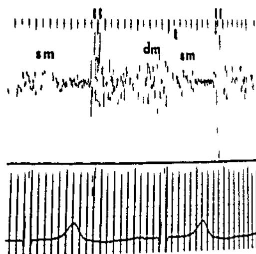


Fig. 2. Case 2—Rheumatic carditis in a 12 year old girl. Systolic murmur in decrescendo. A middiastolic murmur lasting through the presystolic phase. Symbols as in Fig. 1.

murmur and the lack of opening snap allowed us to exclude mitral stenosis.

The final conclusion was: functional diastolic rumble (Carey Coombs murmur), apical systolic murmur of moderate mitral insufficiency, basal diastolic murmur of moderate aortic insufficiency. The murmurs of valve insufficiency were probably related to valve ring dilatation. The clinical picture together with the graphic tracings led to the diagnosis of acute rheumatic carditis.

Case 3. A 19 year old man with rheumatic aortic insufficiency had a severely enlarged heart mostly due to left ventricular dilatation. There was a prolonged P-R interval (0.21 sec.). On auscultation, both a crescendo-decrescendo systolic murmur and an early diastolic blowing murmur were heard at the base. At the apex there was a diastolic presystolic rumble similar to that of mitral stenosis.

The phonocardiogram was simultaneously recorded at the base and apex. The apical tracing (Fig. 3), in addition to vibrations transmitted from the base, showed a high frequency third sound and a diastolic presystolic murmur. The latter was not typically in crescendo as in mitral stenosis and was not preceded by an opening snap. Records taken at the left sternal border showed an early diastolic murmur of high frequency.

The conclusion was: aortic insufficiency, Austin Flint murmur, aortic flow murmur. Cardiac catheterization excluded mitral stenosis. Angiocardiography revealed severe aortic insufficiency and minimal mitral insufficiency.

Case 4. This was a 26 year old woman with a heart markedly enlarged to the left, and both an apical pansystolic murmur and a basal early diastolic decrescendo murmur. There was also a loud prolonged sound in diastole that gave rise to a suspicion of mitral stenosis in addition to mitral and aortic insufficiency. The ECG showed evidence of left ventricular hypertrophy, and Grade 1 A-V block (P-R = 0.36 sec.).

The phonocardiogram with high frequency filtra-

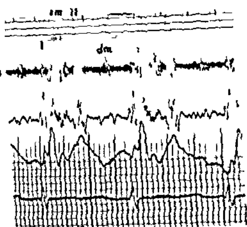


Fig 6 Case 6—High and low frequency functional diastolic murmurs in a 59 year old man with hypertensive heart disease and atrial septal defect The upper tracing is an acceleration tracing at 100 to 400 Hz which shows middiastolic high frequency murmur and diamond shaped systolic murmur The central tracing is an unfiltered velocity tracing which shows low frequency third and fourth sounds The next tracing is an apex cardiogram The lowest tracing is an electrocardiogram

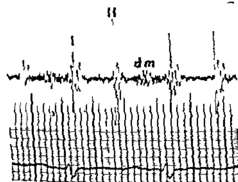


Fig. 7 Case 7—Middiastolic presystolic rumble in a 59 year old woman with atrial septal defect (secundum type) The phonocardiogram was recorded at the apex without a filter

of the sternum There was a Grade 2/6 systolic murmur over the midprecordium and a third sound

The phonocardiogram recorded in a low frequency band (Fig 10) showed good quality of the heart sound, a barely visible systolic murmur and a low frequency diastolic rumble of large voltage starting late after the second sound and terminating in presystole The tracing recorded at higher frequency band revealed a close splitting of the second sound with a large pulmonary component

The diagnosis was chronic cor pulmonale and functional diastolic murmur of the right heart.

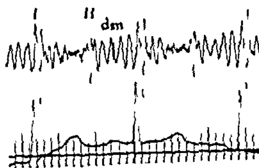


Fig 8 Case 8—Low frequency diastolic rumble in a 56-year old man with alcoholic cardiomyopathy The tracing was recorded at the apex and is a displacement tracing at 10 to 40 Hz.

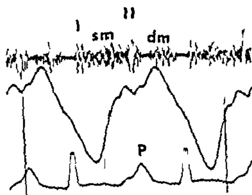


Fig 9 Case 9—Middiastolic high frequency murmur in a 39 year old man with chronic cor pulmonale The upper tracing is a velocity tracing with high pass filter at 400 Hz (slope 24 db per octave) which reveals a pansystolic murmur of tricuspid insufficiency and middiastolic murmur The central tracing is a jugular tracing that shows a sharp rise in systole a late V wave and a plateau typical of tricuspid insufficiency

Case 11 This patient was a 63 year old man with a history of hypertension and coronary heart disease (angina pectoris) In the last few months evidence of left ventricular failure had been present The ECG showed a Grade 1 A V block and evidence of left ventricular hypertrophy and strain

Auscultation disclosed a Grade 1/6 pansystolic murmur and a Grade 2/6 diastolic rumble at the apex a Grade 2/6 systolic ejection murmur and a Grade 1/6 blowing diastolic murmur at the base

The phonocardiogram recorded in a medium low frequency band at the apex (Fig 11) revealed a regular pansystolic murmur a few decrescendo vibrations in early diastole and a presystolic murmur that was in crescendo in some cycles At the base there was a crescendo-decrescendo systolic murmur and a minimal decrescendo diastolic murmur

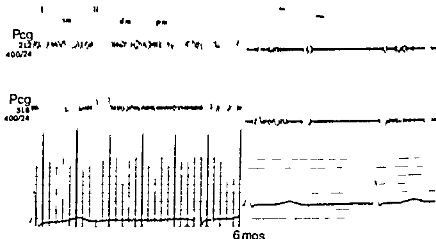


Fig 5 Case 5—High frequency functional diastolic and presystolic murmur both at base (upper tracing) and apex (middle tracing) in a 10 year old boy with sickle cell anemia The tracings at left were recorded during a crisis the tracings at right six months later

The phonocardiogram (Fig 6) recorded over the fourth left intercostal space close to the sternum showed both a third and a fourth sound of low frequency It also showed a very large diamond shaped systolic murmur and a diastolic presystolic murmur of high frequency The diastolic murmur was different from that of mitral stenosis on account of its high frequency the lack of an opening snap and the fact that it was recorded over a wide area of the precordium

On the basis of the clinical electrocardiographic roentgenological and phonocardiographic data the diagnosis of atrial septal defect and hypertensive heart disease was made This diagnosis was subsequently confirmed by cardiac catheterization and angiography

Case 7 This was a 39 year old housewife who came to observation because of progressively increasing exertional dyspnea Pulse rate and blood pressure were normal The heart was of normal size on percussion There was a Grade 1/6 systolic murmur over the second left intercostal space and a wide fixed splitting of the second sound In diastole a third sound was described The x ray showed right heart and pulmonary artery enlargement The ECG showed right axis deviation and evidence of right ventricular hypertrophy

The phonocardiogram confirmed that there was a fixed but narrow splitting of the second sound and a faint systolic murmur It also demonstrated a mid diastolic murmur with presystolic accentuation (Fig 7) The final diagnosis was atrial septal defect

Cardiac catheterization performed in another hospital confirmed that there was an uncomplicated atrial shunt (secundum type)

Case 8 This patient was a 56 year old man with a history of chronic alcoholism and a recent onset of congestive failure The heart was severely enlarged both to the right and the left on percussion and x ray revealed that all chambers were enlarged On auscultation a Grade 1 systolic murmur of high pitch and a low grade low pitched diastolic rumble were heard The ECG was normal except for sinus tachycardia

The phonocardiogram recorded in the low frequency range showed a pandiastolic series of vibrations (Fig 8) This was considered as a functional diastolic rumble

Cardiac catheterization showed a moderate increase in the end diastolic pressure of both ventricles and no evidence of mitral stenosis The final diagnosis was alcoholic cardiomyopathy

Case 9 This patient was a 39 year old Negro man with a history of active pulmonary tuberculosis. Physical examination and chest films revealed active TB of the lungs with multiple infiltrates The liver was palpable two fingerbreadths below the costal margin and was pulsatile The jugular veins were distended and pulsatile The heart was enlarged to both the right and the left The first sound was faint the second sound was loud Both a Grade 2/6 pansystolic murmur and a Grade 2/6 middiastolic rumble were audible over the midprecordium with poor transmission to the apex The ECG showed evidence of right ventricular hypertrophy and strain and tall P waves in Leads II III and aV$_F$ The ECG also showed a prolonged P R interval (0 24 sec.)

The apex phonocardiogram recorded in the low frequency range (not shown) revealed a large irregular complex in diastole (summation gallop) In the high frequency range (Fig 9) it showed the pansystolic murmur and a middiastolic murmur well separated from both the previous second sound and the following first sound

The jugular tracing showed an obvious wave of regurgitation (Fig 9)

The conclusion was chronic cor pulmonale relative tricuspid insufficiency and functional diastolic murmur of the right heart

Case 10 This 38 year old woman had a history of exertional dyspnea for several months She had a pulse of 110 and a blood pressure of 106/78 Several episodes of severe sudden dyspnea with vague chest pain had occurred in the past and raised the question of multiple pulmonary embolizations. The apex was in the sixth left intercostal space 2 cm. to the left of the midclavicular line The first sound was normal the second sound was very loud at the left

sion of such criteria This will be done below

The phonocardiographic criteria are as follows

1 *A wide area of recording of a diastolic murmur* or recording it in the second or third left intercostal space is in favor of a functional murmur This fact can be explained by severe ventricular enlargement

2 *Wide splitting of the second sound* is against mitral stenosis Cor pulmonale congenital shunts or severe right heart failure should be considered instead

3 *High frequency of the murmur* (soft blowing murmur on auscultation) is unusual in mitral stenosis In a special study devoted to this problem[25] we found high frequency vibrations in only 12 per cent of the cases studied by phonocardiography

4 The murmur of mitral stenosis is frequently initiated by an *opening snap* This may be absent however in cases with very severe narrowing of the mitral valve often revealed by the finding of calcification on the x ray If there is no evidence of severe mitral stenosis (clinical roentgenological or electrocardiographic data plus typical history) the lack of opening snap is against mitral stenosis An opening snap can be found in exceptional cases of pure mitral insufficiency It is usually followed by a very large third sound Considering the various exceptions pro and con a moderate importance should be given the lack of opening snap against mitral stenosis

5 *High voltage of the murmur* This is usually not appreciated by auscultation on account of the low frequency of the vibrations which are often close to or even below the threshold of the auditory system In certain cases a barely audible murmur will appear in the tracing (with adequate filtration) as nearly as large or larger than the second sound Cases of mitral stenosis with high voltage of the middiastolic murmur are extremely rare and are probably cases in which severe left ventricular damage due to concurrent processes adds a functional element to the organic murmur High voltage is in favor of a functional rumble and against mitral stenosis

6 *Wide separation of the murmur from the previous second sound* The murmur of mitral stenosis starts with the beginning of left ventricular filling be this marked or not by an opening snap A functional rumble usually starts later and its onset is very often marked by a large third sound Thus the former starts generally from 60 to 120 msec after the aortic component of the second sound while the latter starts from 130 to 180 msec after such component Late start of the middiastolic rumble is in favor of a functional rumble and against mitral stenosis

7 *Middiastolic rumble without presystolic murmur in the presence of sinus rhythm* While functional presystolic murmurs may occur a functional diastolic rumble without presystolic accentuation is more common In mitral stenosis with sinus rhythm if there is a middiastolic rumble there is usually also a presystolic murmur Thus the presence of an isolated middiastolic rumble without atrial fibrillation should be considered at least as an atypical finding of mitral stenosis

8 *Presystolic murmur that is not in crescendo* In mitral stenosis with sinus rhythm the presystolic murmur is typically in crescendo An exception is represented by patients with a very long conduction time Functional murmurs in subjects with a normal P R interval may have a sharp separation from the following first sound

9 *Large third sound or fourth sound* A patient with mitral stenosis nearly never has a large third sound If there is a fourth sound at low frequency and a presystolic murmur at high frequency the stenosis is mild A functional diastolic murmur starts very often with a large or even gigantic third sound It may be followed by a fourth sound Thus large diastolic sounds are usually evidence of a functional diastolic murmur

10 *Effect of amyl nitrite inhalation* This functional test very often increases the murmur of mitral stenosis by causing tachycardia It has been stated that it would decrease the Austin Flint murmur[29] but we have found such a decrease only in some cases Therefore it is difficult to assign a definite value to the results of this test

Summary

The history of functional diastolic murmurs is reviewed These murmurs are defined as murmurs not caused by valve ste

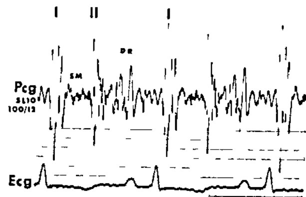


Fig *10* Case 10—Middiastolic rumble (*DR*) of the right ventricle at apex in a 38 year old woman with chronic cor pulmonale

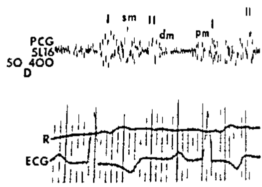


Fig *11* Case 11—Diamond shaped systolic murmur early diastolic murmur and functional presystolic murmur (*DM*) in a 63 year old hypertensive man with coronary heart disease left heart failure and Grade 1 A V block There was also a minimal aortic insufficiency of an atherosclerotic nature

The final conclusion was coronary and hypertensive heart disease possible papillary muscle dysfunction with mitral insufficiency functional diastolic murmur related to left ventricular failure and possibly to ventricular dyssynergy The minimal aortic insufficiency considered as related to atherosclerosis may have been an additional factor

General considerations

The normal heart of a young person has already minimal, inaudible low frequency diastolic vibrations at the apex that can be recorded by means of adequate phonocardiographs [6,27] These vibrations may occasionally become larger and reach the threshold of audibility if there is an overactive cardiovascular system (from exercise after inhalation of amyl nitrite hyperkinetic syndrome [25])

The cause of these vibrations can only be speculated upon They are most likely arising in the left ventricular wall during its distension as suggested by the fact that they frequently start with a large third sound and represent after vibrations of this sound

The murmur of mitral stenosis is caused by the difference in caliber between the mitral valve and the left ventricle Thus it is related to eddies which start at the valve and spread from the inflow tract toward the apex The vibrations of the blood are transmitted to the left ventricular wall and from this, to the chest wall

Functional diastolic rumbles are usually encountered when one of the ventricles (most commonly the left, occasionally the right) is severely dilated when its filling is abnormally large (caused by valve insufficiency or shunts), when its pressure is high (from hypertensive heart disease or cor pulmonale) and especially if the ventricular wall is damaged (from myocarditis or cardiomyopathy coronary heart disease especially after infarcts, and even more if there is a ventricular aneurysm) or is in a state of failure

The mechanism of these murmurs is still in question More rapid and greater filling (from valve insufficiency or shunts) would increase the diastolic vibrations of the wall High pressure would often alter the diastolic tension (from moderate to severe increase of the end diastolic pressure, often associated with strain or failure) Left ventricular damage from any cause would cause uneven compliance and uneven rapidity of filling of various sections of the left ventricle and this may be a cause of murmurs Whether the old concept of ' relative mitral stenosis ' (normal mitral opening large ventricle) is still valid we do not know Probably such a concept should be abandoned because the vibrations are usually found over a much larger area than in organic stenosis

Differential diagnosis between functional diastolic murmurs and the murmur of mitral stenosis

Our experience in the study of functional diastolic murmurs dating from 1950 [18] led us to suggest certain differential data based on differences in phonocardiographic tracings [20] The experience of the last 20 years indicates the need for a revision and exten

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff and Julian Frieden

Medical treatment of angina pectoris III. Pharmacology of sublingual nitrites as antianginal drugs

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Coronary vasodilators have been advocated for the treatment of angina pectoris due to coronary artery disease. Although a coronary vasodilator drug might dilate collateral vessels, it is difficult to conceive of a drug producing vasodilatation in diseased sclerotic vessels in preference to more distensible vessels.[1] In fact, one should be concerned that angina might even be made worse in some patients by the vasodilator drug diverting blood from ischemic areas in the myocardium to other areas in which the vessels are capable of vasodilatation. Moreover, a drop in the systemic blood pressure induced by the vasodilator drug reduces the perfusion of the diseased sclerotic vessels. Hypoxia itself is also the best coronary vasodilator, and maximum vasodilatation probably occurs during an attack of angina pectoris. Therefore, it is not surprising that vasodilator drugs have been found to be ineffective in the treatment of angina pectoris.[2,3]

The mechanism of action of the nitrites in the relief of angina pectoris is not clearly established. Although sublingual nitroglycerin and other nitrites relax vascular smooth muscle and produce coronary vasodilatation in normal man, these drugs do not increase coronary blood flow in patients with coronary artery disease at rest[4-7] or during exercise.[6] Moreover, the fall in systemic blood pressure induced by nitrites may, by decreasing coronary arterial perfusion pressure, actually decrease the myocardial oxygen supply.

Sublingual short-acting nitrites such as nitroglycerin may be effective antianginal agents because they cause a decrease in the myocardial oxygen demand by the following mechanisms. Sublingual nitroglycerin reduces venous tone, causing pooling of blood in the peripheral veins[8] and a decrease in cardiac output, stroke volume, and ventricular volume.[9] The fall in left ventricular end-diastolic pressure both at rest and during exercise after nitroglycerin, in the absence of a change in left ventricular compliance, also suggests a decrease in left ventricular volume.[6] The reduction in the size of the heart by LaPlace's law decreases the intramyocardial tension, reducing the myocardial oxygen requirement. Sublingual nitroglycerin, by causing arteriolar dilatation,[8] also

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nosis, though usually connected with severe changes of cardiovascular dynamics

The phonocardiograms of 11 patients are presented and clinical and laboratory data of these patients are discussed. The mechanism of the functional diastolic murmurs is discussed, and differential phonocardiographic criteria are presented.

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lowers the arterial pressure By reducing systolic intraventricular pressure and the resistance to ventricular ejection, the myocardial oxygen demand is further decreased A reduction in the arterial pressure, cardiac output, and stroke volume causes a decrease in external work performed by the left ventricle, leading to a reduction in myocardial oxygen consumption

However nitroglycerin also increases the resting heart rate and the tension-time index was not significantly altered by nitroglycerin in patients with angina pectoris at rest and during exercise compared to the control periods [8] A significant increase in systolic ejection rate despite a lower level of left ventricular end diastolic pressure and volume also suggests that myocardial contractility was probably increased during exercise after nitroglycerin [8] This increase in myocardial contractility increases the myocardial oxygen requirement

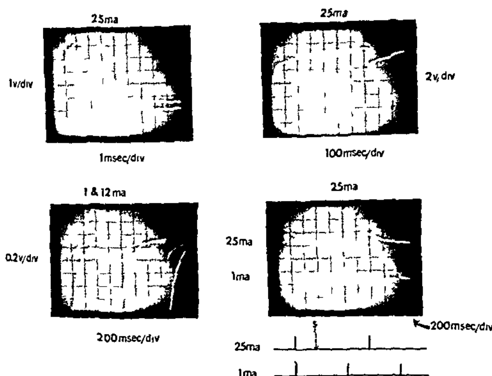
Goldstein and his associates[10] reported that in patients with angina pectoris due to coronary artery disease who performed upright exercise sublingual isosorbide dinitrate tested as a short acting nitrite produced lower systolic and mean blood pressures a faster heart rate a shorter ejection time and a slightly reduced over all heart size Sublingual nitroglycerin and sublingual isosorbide dinitrate produced very similar alterations in the circulatory response to upright exercise in their patients with angina pectoris The duration of action of sublingual isosorbide dinitrate was also similar to that of sublingual nitroglycerin in their patients with angina

We reported[11] that in patients with angina pectoris due to coronary artery disease who performed upright exercise one hour after administration of sublingual medication there was no significant difference in the group s mean systolic or diastolic blood pressure, heart rate or product of systolic blood pressure and heart rate at rest or immediately after exercise induced angina during treatment of sublingual isosorbide dinitrate compared to sublingual placebo Goldstein and his associates'[10] data and our data provide hemodynamic evidence for the ineffectiveness[10,11] of sublingual isosorbide dinitrate as a long acting antianginal agent

Horwitz and his co workers[12] found that sublingual nitroglycerin induced a significant increase in coronary blood flow to diseased regions in patients with angina pectoris due to coronary artery disease These investigators concluded that sublingual nitroglycerin is efficacious as an antianginal agent partially because it causes redistribution of coronary blood flow so that a greater portion of the total coronary blood flow is delivered to ischemic regions, in addition to its ability to decrease myocardial oxygen demand However, Wang and his associates[13] reported that a constant infusion of nitroglycerin, while increasing total coronary blood flow decreased left anterior descending coronary arterial flow in 7 of 12 dogs (58 per cent) with a stenosed left anterior descending coronary artery, did not change left anterior descending flow in 3 of these 12 dogs (25 per cent), and increased left anterior descending flow in only 2 of these 12 dogs (17 per cent)

Dipyridamole has been demonstrated to be a powerful coronary vasodilator[8,14] However unlike short acting nitrites such as nitroglycerin dipyridamole does not reduce the myocardial oxygen demand in patients with coronary artery disease Dipyridamole has also been shown in several double blind studies to be no more effective than placebo in the treatment of angina pectoris due to coronary artery disease[8,14] There is no good clinical evidence documenting that any antianginal drug is effective because it is a coronary vasodilator

In summary, coronary vasodilators do not increase coronary blood flow in patients with coronary artery disease nor reduce myocardial oxygen demand Although sublingual short acting nitrites such as nitroglycerin do not increase the oxygen supply to the myocardium, they may be effective as antianginal agents due to a reduction in myocardial oxygen requirement This decrease in myocardial oxygen demand is primarily caused by peripheral vasodilatation causing a reduction in left ventricular volume Long acting nitrites and other coronary vasodilators do not appear either to increase the oxygen supply to the myocardium or to decrease the myocardial oxygen demand and therefore are ineffective as antianginal agents



Fi 1 Voltage wave forms of the 5840 Medtronic demand pacemaker connected to a USCI catheter with elec trodes 1 cm. apart. All measurements were recorded with the catheter in normal saline without additional re ti e lo d The upper panel on the left hows the duration of the pacemaker impulse at 1 6 msec and the presei ce of a relatively large t me chan ing voltage after the initial impulse The upper pan l on the r ght also nows the after potent al between the pacemaker impulses The lower panel on the left hows the varying co figurat ons of the after potential according to the e ergy settings on the pacemaker The pacemaker rates are identical at 1 and 12 mA and the initial pul es with both settings are superimpo ed at the lower end of the ho ogr ph. Note that the pace naker after potential belonging to the 12 mA di charge (on the right of the o e corre pond ng with the 1 mA setting) contains a sharper dv/dt segment out ide the refractory period of 30 msec. The lower panel on the right hows the doul le reset phenomenon at 25 mA The signal provided by the after potential recycles the pacemaker with one full escape interval (v = volt div = divi ion)

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Reflex vasodilatation and Raynaud's disease

As the writer i l atc l i i n e rl er rt le there is no dru available th t pec fically dilates th ve sels of the fingertips. Vasodilator drugs dilate most or all blood vessels of the body Such a vasod latat on could readily shift blood from the fingert ps to the larg vascular reservo of tl e l ody conceivably re ult ng n a paradox cal therapeut c re ponse To produce s gn ficant dilatation of the digital vessels the patient needs only to keep the body warm to the point of sweating by wearing coats sweaters gloves

"Double reset" of demand pacemakers

Beller and Pupillo recently documented the unusual behavior of the 5840 Medtronic demand pacemaker when used at energy levels over 12 mA with a particular USCI catheter.[1] They observed in this situation intermittent slowing of the pacemaker rate and suggested that the abnormality was related to the demand function since the pacemaker rate remained constant during fixed rate pacing.

This disturbance has been and remains a potential problem in the design of all demand pacemakers. When a pacemaker delivers a 1 or 2 msec stimulus it charges the electrode tissue interface to a large DC potential.[2] Dissipation of this large voltage (generally over 1,000 mV) between pacemaker pulses creates a time changing voltage (pacemaker "after potential") that may be sensed by the pacemaker as it comes out of its refractory period[2,5] (Fig. 1).

The electrocardiograms in Beller and Pupillo's paper show in strips A to E ventricular pacing by a 5840 Medtronic pacemaker with an automatic interval of approximately 640 msec. In strip E during pacing at 12 mA the interval between consecutive pacemaker impulses lengthened intermittently to a constant value of 940 to 960 msec. Thus the pacemaker appeared to sense a signal 300 to 320 msec after the pacemaker stimulus or about 50 to 70 msec after its delivery refractory period which usually lasts 250 msec in this particular model.[2] This is consistent with sensing the pacemaker "after potential" just outside the delivery refractory period.[2,3] Since for this pacemaker the true escape interval equals the automatic interval the 50 to 70 msec delay represents the time required for the voltage decay wave form to activate the demand mechanism and may also reflect intrinsic delays in the circuit according to the polarity of the incoming signal.[2]

The manufacturers have alerted the medical profession of this particular problem and offered to modify the pacemakers to eliminate this characteristic.[6] Although the manufacturers suggested that this phenomenon could be compensated for by adjusting the rate dial until the required rate was achieved,[6] we feel that this approach is sometimes unsatisfactory for the following reasons: (1) The disturbance is often intermittent. Thus adjustment of the pacemaker rate during continuous "over sensing" of the pacemaker "after potential" may lead to undesirable rapid pacing rates when the pacemaker "after potential" can no longer provide an adequate signal to suppress the pacemaker. (2) Recycling of this particular pacemaker at the end of its delivery refractory period doubles its effective refractory period to about 500 msec since its sensing and delivery refractory periods are equal.[2] This relatively long refractory period may lead to spontaneous beats being unsensed by the pacemaker, a complication we have actually observed.

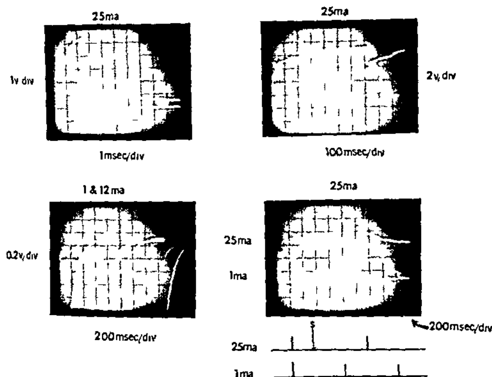
We have never considered the "double reset" characteristic of the 5840 Medtronic pacemaker potentially dangerous as did Beller and Pupillo, probably because we have always been able to deal with it. The frequent intermittency of the disturbance over 12 mA implies that the signal is marginal and often incapable of being sensed. Therefore we have always corrected the problem by a slight reduction of the input sensitivity of the pacemaker (middle dial) provided the voltage of the ventricular electrogram is well above 2 mV. When the QRS signal is relatively low we would not recommend reduction of the input sensitivity.

We have observed, as did Beller and Pupillo, the "double reset" phenomenon with USCI pacing catheters with electrodes 1 cm apart but have seen it occasionally when the electrodes are 2 cm apart and also with the new Medtronic 5 French 6,00 catheter with electrodes 2.8 cm apart. Many examples of apparent sensing of the T wave of paced ventricular beats may indeed represent sensing of the "after potential" with or without the addition of T wave voltage.

The "double reset" problem from sensing the pacemaker "after potential" has not been restricted to Medtronic pacemakers and has been observed to occur with demand pacemakers from several other manufacturers.[5] The approach to solving this problem constitutes important considerations in the design of demand pacemakers and includes (1) using appropriate pacing catheters such as the Medtronic 5821 with a 5840 pacemaker to avoid the larger circuit capacitance when unsuitable catheters are used (a larger capacitance will be less completely discharged during the refractory period and thus more prone to generate a significant signal outside the refractory period), (2) better low frequency rejection circuitry, (3) reduction of the pacemaker sensitivity easily accomplished manually on the external units, (4) increasing the delivery refractory period so that it will contain the large dv/dt segment of the "after potential", (5) changing the output time constant of the pacemaker electrode system so that the "after potential" discharge occurs faster.

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Beller and Pupillo recently documented the unusual behavior of the 5840 Medtronic demand pacemaker when used at energy levels over 12 mA with a particular USCI catheter.[1] They observed in this situation intermittent slowing of the pacemaker rate and suggested that the abnormality was related to the demand function since the pacemaker rate remained constant during fixed rate pacing.

This disturbance has been and remains a potential problem in the design of all demand pacemakers. When a pacemaker delivers a 1 or 2 msec. stimulus, it charges the electrode tissue interface to a large DC potential.[2] Dissipation of this large voltage (generally over 1,000 mV) between pacemaker pulses creates a time-changing voltage (pacemaker "after potential") that may be sensed by the pacemaker as it comes out of its refractory period[3,4] (Fig. 1).

The electrocardiograms in Beller and Pupillo's paper show in strips A to E ventricular pacing by a 5840 Medtronic pacemaker with an automatic interval of approximately 640 msec. In strip E during pacing at 12 mA, the interval between consecutive pacemaker impulses lengthened intermittently to a constant value of 940 to 960 msec. Thus, the pacemaker appeared to sense a signal 300 to 320 msec. after the pacemaker stimulus or about 50 to 70 msec. after its delivery refractory period which usually lasts 250 msec. in this particular model.[2] This is consistent with sensing the pacemaker "after potential" just outside the delivery refractory period.[2,3] Since for this pacemaker the true escape interval equals the automatic interval, the 50 to 70 msec. delay represents the time required for the voltage decay wave form to activate the demand mechanism and may also reflect intrinsic delays in the circuit according to the polarity of the incoming signal.[2]

The manufacturers have alerted the medical profession of this particular problem and offered to modify the pacemakers to eliminate this characteristic.[6] Although the manufacturers suggested that this phenomenon could be compensated for by adjusting the rate dial until the required rate was achieved,[6] we feel that this approach is sometimes unsatisfactory for the following reasons: (1) The disturbance is often intermittent. Thus, adjustment of the pacemaker rate during continuous "over-sensing" of the pacemaker "after potential" may lead to undesirable rapid pacing rates when the pacemaker "after potential" can no longer provide an adequate signal to suppress the pacemaker. (2) Recycling of this particular pacemaker at the end of its delivery refractory period doubles its effective refractory period to about 500 msec. since its sensing and delivery refractory periods are equal.[2] This relatively long refractory period may lead to spontaneous beats being unsensed by the pacemaker, a complication we have actually observed.

We have never considered the "double reset" characteristic of the 5840 Medtronic pacemaker potentially dangerous as did Beller and Pupillo, probably because we have always been able to deal with it. The frequent intermittency of the disturbance over 12 mA implies that the signal is marginal and often incapable of being sensed. Therefore, we have always corrected the problem by a slight reduction of the input sensitivity of the pacemaker (middle dial) provided the voltage of the ventricular electrogram is well above 2 mV. When the QRS signal is relatively low, we would not recommend reduction of the input sensitivity.

We have observed, as did Beller and Pupillo, the "double reset" phenomenon with USCI pacing catheters with electrodes 1 cm. apart but have seen it occasionally when the electrodes are 2 cm. apart and also with the new Medtronic 5 French 6100 catheter with electrodes 2.8 cm. apart. Many examples of apparent sensing of the T wave of paced ventricular beats may indeed represent sensing of the "after potential" with or without the addition of T wave voltage.

The "double reset" problem from sensing the pacemaker "after potential" has not been restricted to Medtronic pacemakers and has been observed to occur with demand pacemakers from several other manufacturers.[8] The approach to solving this problem constitutes important considerations in the design of demand pacemakers and includes: (1) use of appropriate pacing catheters such as the Medtronic 5821 with a 5840 pacemaker to avoid the larger circuit capacitance when unsuitable catheters are used (a larger capacitance will be less completely discharged during the refractory period and thus more prone to generate a significant signal outside the refractory period); (2) better low frequency rejection circuitry; (3) reduction of the pacemaker sensitivity, easily accomplished manually on the external units; (4) increasing the delivery refractory period so that it will contain the large dv/dt segment of the "after potential"; (5) changing the output time constant of the pacemaker electrode system so that the "after potential" discharge occurs faster.

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Assessment of LVEDP from right heart pressures during atrial pacing

Recent reports have described the use of right atrial pacing through pacing induced changes in left ventricular end-diastolic pressure (LVEDP) and stroke work to determine left ventricular function in patients with coronary artery disease.[1,2] When pulmonary vascular resistance is normal, a good correlation frequently exists between pulmonary artery end-diastolic pressure, pulmonary wedge "A" wave or mean pressure, and the LVEDP.[3-6] If this relationship held true during atrial pacing, then pulmonary artery and wedge pressures could be used to estimate LVEDP and, in association with systemic arterial pressures and cardiac output, LV function curves could be determined easily in the coronary care unit. This would be a natural extension of the hemodynamic studies which are being used presently in the early evaluation of the patient following myocardial infarction,[7] and would eliminate the need to obtain left heart pressures.

In order to evaluate this possibility, simultaneous right heart and left ventricular end-diastolic pressures were recorded in patients with coronary artery disease during atrial pacing studies as previously described.[1] Table I discloses that at a control heart rate of 81 ± 3 beats per minute, pulmonary artery end-diastolic and wedge pressures gave a fairly accurate estimate of LVEDP. However, as heart rate was gradually increased by atrial pacing to an average of 130 ± 6 beats per minute, right heart pressures changed insignificantly while LVEDP declined in a linear fashion. Therefore, significant differences existed between these right heart pressures and LVEDP and at pacing rates over 100 they could not be used to estimate LVEDP. With the interruption of pacing, the right heart and left ventricular end-diastolic pressures resumed their correlation within one to two beats. This lack of correlation at rapid rates is probably related to the increase in PR interval with atrial pacing (Table I) and a superimposition of the A and V waves in the left atrial and consequently the wedge pressures.[8,9] It is probable that this divergence of right heart and LV end-diastolic pressures would also occur during any spontaneous atrial tachycardia with prolonged PR interval and certainly would be present when atrial pacing is employed to suppress ventricular arrhythmias.[4] Therefore, under these circumstances as well as in an attempt to determine myocardial function, left heart pressures must be measured.

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Table I. Hemodynamics during atrial pacing

	HR	PR	PAW	PAW A	LVEDP(1)	PAEDP	LVEDP(2)
Control	81 ± 3	0.16 ± 0.01	11 ± 2	16 ± 4	12 ± 2	14 ± 2	13 ± 3
Pacing	130 ± 6†	0.22 ± 0.01†	13 ± 2	17 ± 3	6 ± 2†	18 ± 3	9 ± 2

HR = heart rate in beats per minute; PR = PR interval in seconds; PAW A = pulmonary artery wedge A wave pressures; LVEDP = left ventricular end-diastolic pressure; PAEDP = pulmonary artery end-diastolic pressure. All values are means ± standard error of the mean and pressures in mm Hg.

†Significant difference ($P < 0.05$) between control and pacing values. PAW, PAW A, and PAEDP during pacing were all significantly greater than LVEDP during pacing. PAW and PAW A must be compared to LVEDP(1) and PAEDP to LVEDP(2).





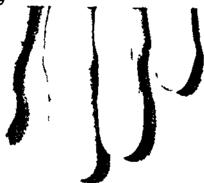


Fig. 1. Raynaud's disease of the fingertips in a 54 year old Caucasian woman who was suffering excruciating digital pain. The ischemic and necrotic tissue healed nicely merely by keeping the body, hands, and feet warm at all times with warm clothing and loose fleece-lined or woolen gloves. The practice of keeping the body warm is being continued, the lesions remain healed, and the patient is symptom free.





Fig. 2. Raynaud's disease of the fingertips in a 38 year old Caucasian woman who was suffering excruciating digital pain. The ischemic and necrotic tissue healed following reflex digital vasodilatation produced by keeping the body and extremities warm with proper clothing and use of loose warm gloves. Body warmth is being continued, the lesions remain healed, and the patient is free from symptoms.

woolen stockings, mufflers, and other warm clothes and warm bed clothing according to the environmental conditions. It is well known that when the body tends to become too warm there is a fairly intense vasodilatation of all blood vessels of the hands, feet, fingers, and toes in an effort to lose body heat. The patient must avoid touching cold things, exposing himself to cool or cold drafts, getting wet, or doing anything which would result in constriction of the digital vessels. Vibrations, excessive washing of the hands, use of the fingers, and other forms of even mild trauma must, of course, receive serious consideration in therapy.

Figs. 1 and 2 show the results of management of digital disease with reflex digital vasodilatation produced by body and extremital warmth achieved merely by the use of warm clothing. No vasodilator drugs were used in these cases. The digital vasodilatation is produced reflexively on a continuous basis simply by keeping the body warm. The two patients under consideration continue to do well after two and four years, respectively; previous to the periods shown, their disease was rapidly worsening in spite of treatment with vasodilator drugs. It is unnecessary to point out that an intact sympathetic nervous system is necessary for the production of reflex vasodilatation.

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wave form correction which must have required nothing more than drafting board, T square, right angle triangle and divider or compass—almost Euclidean in its constructional simplicity.[3] In Einthoven's method the coordinates of successive points on the electrometer curve were carefully measured and the first derivative of the curve was approximated as the slope of straight lines connecting adjoining pairs of points.[4] His treatment of electrometer records revealed the presence of such common place but previously obscured ECG features as the Q and S waves. This tantalizing glimpse of the future must have served as a powerful stimulus in his efforts to devise a dynamically adequate recorder the string galvanometer.

Combining very old and quite modern instrumentation together in a curious mix we recently retraced some of the steps which Einthoven took in his pursuit of wave form correction. We photographically magnified several fold the published Lead I electrometer record of his subject Mr v. d. W.[4] and taped the enlarged curve to the drum of a computer-driven incremental plotter. A home made optical scanner was mounted in the pen carriage of the plotter. Under program control the scanner traced out the electrometer curve storing the digitized values of deflection in computer memory. The curve corresponding to the first time derivative was determined by numerical differentiation and added to the original curve in an amount sufficient to construct an ECG complex with about the same R/T amplitude ratio which Einthoven achieved in his own treatment of the same material. A cut and try approach was necessary since the decay constant of the electrometer is not stated in the source publication. The numerical equivalent of a high frequency rolloff filter was applied to smooth out the fine notches and discontinuities which are produced by the differentiation of discretized and somewhat grainy data. The original curve taken from Einthoven's paper together with the results of our numerical processing are illustrated in Fig. 1.

Our reconstructed curve differs in some respects from that obtained by Einthoven. For example we find our P wave to be less crisply defined than his, the Q deflection is somewhat less prominent, and the S more prominent. Since the principle of wave form correction is so straightforward and simple of application we surmise that the differences in results are probably due to some distortion of his original curve in the cut which was prepared for publication. Regardless of what the explanation may be the important outcome of our vicarious experience was the restoration of peak R and T amplitudes to an approximately correct relationship and the retrieval of the Q and S deflections from the dynamic morass of the sluggish mercury column.

The valiant pioneering attempts by Burch and Einthoven to achieve records of good dynamic quality were remarkable because of their underlying motivation as well as for their ingenuity. Their work explicitly emphasizes the need for both aesthetic touch technique and a full appreciation of the pertinent principles of instrumentation for accurate physiological recording is to be achieved. We should hope that these lessons from the past would be reflected today more than three quarters of a century later in the quality of record which we demand of ourselves in modern electrocardiographic practice.

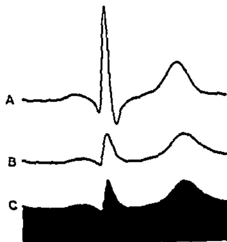


Fig. 1. Application of modern signal processing techniques to wave-form correction of an electrocardiographic complex recorded by Lippmann's capillary electrometer. The lower curve (*C*) is an electrometer recorded Lead I tracing taken from a publication of Einthoven's. The middle curve (*B*) shows a computer produced replica of the original (*C*) converted to digitized form by an optical scanner and drawn to identical scale by an incremental plotter. In the upper curve (*A*) the numerical corrective measures described by Einthoven and G. J. Burch have been employed to recover some of the more rapid signal variations which were obscured by the sluggish dynamic properties of the capillary electrometer. Further discussion in text.

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Einthoven, G. J. Burch, and the capillary electrometer

Human electrocardiography is a venerable art and science Records on human beings were first published by Waller[1] in 1889 Two years earlier he had published records obtained by applying electrodes directly to the exposed rabbit heart Scientific writing being the dispassionate exercise that it is one can only guess the sense of excitement that Waller must have felt when he finally succeeded in recording electrical impulses from an intact subject

At that time and for more than the next decade the electrocardiogram (ECG) was recorded by means of Lippmann s capillary electrometer The electrosensitive element in this device consisted of a mercury–sulfuric acid interface in a vertically mounted glass capillary Application of an electrical potential difference across the phase boundary changed surface tension by a small amount and thus caused microscopic movement of the mercury meniscus Casting a highly magnified shadow of the meniscus on a laterally moving light sensitive plate produced a graphic record of the electrical event Waller s original records are rather indistinct due partly to low signal amplitude and partly to poor photographic contrast between the mercury and sulfuric acid phases This situation improved as techniques developed The capillary electrometer records eventually obtained by Einthoven show relatively adequate signal amplitude and are marvels of photographic clarity

The capillary electrometer was the only device available at the time which could even begin to follow the rapid deflections of the cardiac signal and other electrophysiologic events having similar rates of change Even so it was not fully equal to the task of faithful ECG registration With its large viscous drag due to movement of fluid through a capillary tube and the low ratio of recoil force to mass it could not help but be a sluggish heavily overdamped instrument Indeed viscous drag so greatly dominated the dynamic picture that mass could be disregarded in applying the usual differential equations of motion As a result abrupt application of a constant potential difference fell far short of producing the steplike change which one would expect of a dynamically adequate instrument instead in accordance with theoretical prediction movement of the meniscus traced rather slowly an exponential decay curve in arriving at its new level

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These facts were well known to Einthoven[1] and equally so to G J Burch[2] who worked on the electrical activity of frog skeletal muscle in the Physiological Laboratory at Oxford Both men fully recognized that appreciable amounts of wave form information were being wiped out or buried by the sluggish response of the capillary electrometer and both sought means for restoring the blurred details of signal configuration Einthoven s work appears to have been the more analytical at least to the extent that mathematical formulations were spelled out in detail On the other hand the underlying dynamic principles were implicit in Burch s work and his method of wave form compensation led to the same result Burch s earliest publication on the subject preceded Einthoven s by four years

The dynamic characteristics of the capillary electrometer made it a direct mechanical analogue of the simplest kind of low pass electrical filter Only the direct current component of an impressed signal came through unaltered Time varying components were subject to lag and attenuation with output amplitude of specific sinusoidal content being progressively diminished for increasing frequencies

Both Einthoven and Burch determined the dynamic parameters of the capillary electrometer by examining its response to a step input They found this to be of the form

$$y = a(1 - e^{-bt})$$

where y is position of the meniscus shadow at time t after application of the step input a is the ultimate value of y e is the base of natural logarithms and b is the all important decay constant of the system Einthoven s meticulous measurements showed this relationship to hold true well within the limits of experimental error[3] In principle wave form restoration simply consists of adding to the recorded curve on a point by point basis $1/b$ parts of its first time derivative For example the first derivative of the above response curve to unit step input is

$$y = ab\,e^{-bt}$$

It follows directly from this that

$$y + y/b = a$$

and thus the form of the applied step voltage is theoretically recovered The validity of the method for all kinds of input signals is readily confirmed by the more rigorous forms of mathematical analysis which are in common use today

Burch developed an ingenious graphic method of

structure which tautens abruptly in the wake of the rising ventricular pressure. Is it not reasonable to assume that such a sound is an "opening snap" of the aortic valve?

In summary, therefore, all hemodynamic and direct visual evidence continues to be consistent with the conclusion that the mitral snap is related to *opening* of the valve. We suspect that if Drs. Rodbard and Libanoff would re-examine their own data they, too, might come to a similar conclusion.

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Reply

To the Editor:

Drs. Tavel and Feigenbaum state that "virtually all authorities have accepted the view that the snap is *in some way* (my italics) related to opening of the mitral valve." However, at least six different interpretations of the events after opening of the valve and prior to the snap have been offered by various authors, as indicated in references 21 to 26 in our paper.[1] For example, Ross and Criley state that the snap occurs "at the moment of first flow through the valve," while Tavel and Feigenbaum hold that the mitral valve is open prior to the snap, and that atrial pressure exceeds ventricular pressure for as much as 30 msec. before the snap is generated by the arrest of the motion of opening of the stenotic valve in mid-diastole. The latter mechanism cannot account for the mitral-like snaps heard in many conditions in which there is no mitral stenosis, as in ventricular septal defect, ductus arteriosus, atrial myxoma, or after exertion in some normal subjects (references 21 and 30 to 40 in our paper).[1] Their comment on the murmur of mitral regurgitation is not directly relevant to the question of the snap.

They claim that "direct studies of mitral movement by means of echocardiography and cineangiography" do not support our thesis that the previously opened mitral valve generates the snap as it closes momentarily during early systole. We seriously question the validity of their position, as indicated below.

Echocardiography. Tavel and Feigenbaum state that they have never observed echographic evidence for closure of either the anterior or posterior leaflet during early diastole. Limitations in the technique of echocardiography raise questions concerning their statement. The sonar pulses are held to be a collimated or converging beam, and the echo is assumed to be reflected from specific interface, such as the anterior leaflet of the mitral valve. The actual reflections come from a broad arc of interfaces, and the accumulated echoes for each distance are displayed as an apparent single echo.

At the time of the snap, each of the components of the heart is involved in complex movements. Thus, the runoff of arterial blood causes the aortic root to move superiorly, the septal muscle bundles begin to elongate, the mitral ring moves away from the apex, and the mitral valve leaflets are pushed apart and atrioventricular flow begins as ventricular pressure falls below atrial pressure. The complex geometry of the resulting reflective surfaces and their changes with time diminish the likelihood that a particular portion of the surface of the anterior leaflet can be definitively identified as the sole, or even the major, source of the reflected signal. Zaky, Nasser, and Feigenbaum[4] have recently recognized that a portion of the "mitral valve" movements may be generated by the base of the heart, especially by the mitral valve ring. Strong echoes generated by surrounding extracardiac structures can also seriously complicate the tracing and its interpretation. The orchestra of echoes from many different moving surfaces forces the echocardiographer to direct the beam in various directions through a small intercostal portal until a pattern appears which he believes, on the basis of experience, to be the solo movements of the anterior leaflet of the mitral valve. Slight angulation or change in position of the transducer on the chest wall produces significant changes in the echo wave forms. The decision as to their sources has been stated: "The echoes from the anterior leaflet of the mitral valve are determined by their location and timing with the opening snap." This standard is also reversed: "The opening snap occurs after the sudden onset of (echographic) mitral valve opening."[4] Such internal calibrations do not offer certainty regarding the source of the recorded signals.

An even more serious question is exemplified in Tavel and Feigenbaum's Fig. 1. Their trace may not properly represent the full train of echoes. The successive echoes from the 1,000 impulses per second normally vary greatly in amplitude, suggesting that the interfaces may be changing rapidly. Displays of all of the echoes are usually highly irregular and difficult to analyze.[4] These great irregularities are also evident in current publications.[3]

Much clinical echocardiography avoids the for-

Letters to the Editors

The "closing snap" in mitral stenosis

To the Editor

After reading the article entitled "The mitral closing snap" by Drs Rodbard and Libanoff (AM HEART J 83:19, 1972), our reaction was one of utter consternation. Since at least the early 1930's, when the elegant studies of Margolies and Wolferth clearly defined the characteristics of the mitral "opening snap," virtually all authorities have accepted the view that this snap is in some way related to opening of the mitral valve. Moreover, it appears that the sound is generated at the time that the mitral valve *first reaches* its fully open position, halting its forward movement abruptly.[1-4]

Now Drs Rodbard and Libanoff attempt to debunk this principle by invoking certain pressure findings to support an opposing theory. Before we decide to consider these authors' conclusions very seriously, let us examine their data more closely.

Their observations provide evidence that the mitral valve is open prior to the snap. This does indeed agree with our data[4] and with those of others[1-3] who have shown that the valve has reached maximum opening coincident with the snap. This point occurs about 20 to 30 msec. after the left ventricular pressure drops below the left atrial pressure in early diastole. Therefore, the earliest the snap might be expected to occur would be 20 or 30 msec. earlier—not the entire 80 msec. of isovolumic relaxation (interval between aortic closure and the usual opening snap) as suggested by Rodbard and Libanoff. They then suggest that since the snap ordinarily is so late, the mitral valve must have closed in order to cause the snap. Direct studies of the mitral movement with both cineangiocardiography[3] and echocardiography[1,4] do not support such an assumption. We have looked at literally hundreds of echocardiograms of mitral valve motion in mitral stenosis, and despite this technique's extremely high frequency response (up to 1,000 Hz), we have never observed closure of either the anterior or posterior leaflet in early diastole. All studies simply show that the leaflets have first reached their most open position (Fig. 1) at the time of the snap.

Rodbard and Libanoff go on to state that "the snap is best heard superior to and somewhat to the right of the cardiac apex. This location supports the thesis that the sound may be louder in the atrium than in the ventricle." Unfortunately, one serious flaw in this line of reasoning is provided by the example of mitral regurgitation, which produces a murmur located best in the left atrium. Such a murmur does not ordinarily have a location "to the right and superior to the apex."

Rodbard and Libanoff state that 10 msec. after the snap the atrial pressure rises and forms a notch and rise. This is analogous to the dicrotic notch of the arterial pulse as *closure* of the aortic valve occurs. If this analogy were correct (and we suspect that it is), then one would expect the trough of the atrial

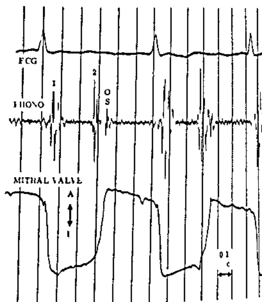


Fig. 1. Phonocardiogram (*middle*) with simultaneous echocardiogram of anterior leaflet of mitral valve (*bottom*) showing the opening snap (*OS*) occurring at the point that the mitral leaflet first reaches its fully open anterior position in early diastole. No closure occurs during diastole.

pressure notch to occur as the mitral leaflets suddenly cease to move *away* from the atrium (toward the ventricle), ending their opening motion. This would be truly analogous to the situation in which the aortic valve leaflets suddenly stop moving away from the aorta (toward the ventricle), reaching, in this instance, the end of their closing movement. The subsequent rise in pressure in the atrium or aorta following each notch would simply be a rebound phenomenon to the sudden cessation of motion.

Rodbard and Libanoff go even further to cast doubt on the thesis that opening motions of the valves are *ever* capable of producing sharp sound. Their analogy here is to liken the mechanism to that of a door suddenly opening. "This movement does not produce sound, whereas closing does produce a sharp transient." Certainly this statement is true of normal doors, but what of the "stenotic" door? Suppose we were to tie a cord from the doorjamb to the doorknob and permit the door to open just half way. This having been done, a quick opening motion would result in the door's opening motion suddenly being arrested in mid-flight; a sound would surely result from this checking motion. In this connection, the mechanism of the ejection click of valvar aortic stenosis provides important insight. Is it too produced by *closure* of the semilunar valve? Certainly not! Accurate cineangiocardiographic hemodynamic studies[5,6] show that a sound is produced as the aortic leaflets reach their maximum (although restricted) open position, forming a sail-like or domed

structure which tautens abruptly in the wake of the rising ventricular pressure. Is it not reasonable to assume that such a sound is an opening snap of the aortic valve?

In summary, therefore, all hemodynamic and direct visual evidence continues to be consistent with the conclusion that the mitral snap is related to opening of the valve. We suspect that if Drs. Podbard and Libanoff would re-examine their own data they too might come to a similar conclusion.

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Reply

To the Editor:

Drs. Tavel and Feigenbaum state that "virtually all authorities have accepted the view that the snap is *in some way* (my italics) related to opening of the mitral valve." However, at least six different interpretations of the events after opening of the valve and prior to the snap have been offered by various authors, as indicated in references 21 to 26 in our paper.[1] For example, Ross and Criley[2] state that the snap occurs "at the moment of first flow through the valve," while Tavel and Feigenbaum hold that the mitral valve is open prior to the snap and that atrial pressure exceeds ventricular pressure for as much as 30 msec. before the snap is generated by the arrest of the motion of opening of the stenotic valve in midflight. The latter mechanism cannot account for the mitral snaps heard in many conditions in which there is no mitral stenosis, as in ventricular septal defect, ductus arteriosus, atrial myxoma, or after exertion in some normal subjects (references 21 and 30 to 40 in our paper).[1] Their comment on the murmur of mitral regurgitation is not directly relevant to the question of the snap.

They claim that "direct studies of mitral movement by means of echocardiography and cineangiography" do not support our thesis that the previously opened mitral valve generates the snap as it closes momentarily during early systole. We seriously question the validity of their position, as indicated below.

Echocardiography. Tavel and Feigenbaum state that they have never observed echographic evidence for closure of either the anterior or posterior leaflet during early diastole. Limitations in the technique of echocardiography raise questions concerning their statement. The sonar pulses are held to be a collimated or converging beam and the echo is assumed to be reflected from specific interfaces such as the anterior leaflet of the mitral valve. The actual reflections come from a broad arc of interfaces and the accumulated echoes for each distance are displayed as an apparent single echo.

At the time of the snap each of the components of the heart is involved in complex movements. Thus, the runoff of arterial blood causes the aortic root to move superiorly, the septal muscle bundles begin to elongate, the mitral ring moves away from the apex, and the mitral valve leaflets are pushed apart and atrioventricular flow begins as ventricular pressure falls below atrial pressure. The complex geometry of the resulting reflective surfaces and their changes with time diminish the likelihood that a particular portion of the surface of the anterior leaflet can be definitively identified as the sole or even the major source of the reflected signal. Zaky, Nasser, and Feigenbaum[4] have recently recognized that a portion of the mitral valve movements may be generated by the base of the heart, especially by the mitral valve ring. Strong echoes generated by surrounding extracardiac structures can also seriously complicate the tracing and its interpretation. The orchestra of echoes from many different moving surfaces forces the echocardiographer to direct the beam in various directions through a small intercostal portal until a pattern appears which he believes, on the basis of experience, to be the solo movements of the anterior leaflet of the mitral valve. Slight angulation or change in position of the transducer on the chest wall produces significant changes in the echo wave forms. The decision as to their sources has been stated: "The echoes from the anterior leaflet of the mitral valve are determined by their location and timing with the opening snap." This standard is also reversed: "The opening snap occurs after the sudden onset of (echographic) mitral valve opening."[4] Such internal calibrations do not offer certainty regarding the source of the recorded signals.

An even more serious question is exemplified in Tavel and Feigenbaum's Fig. 1. Their trace may not properly represent the full train of echoes. The successive echoes from the 1,000 impulses per second normally vary greatly in amplitude, suggesting that the interfaces may be changing rapidly. Displays of all of the echoes are usually highly irregular and difficult to analyze. These great irregularities are also evident in current publications.[4]

Much clinical echocardiography avoids the fore-

going difficulties by dropping the deviant signals In oscilloscopic display selective filtration[6] smoothes the returning signal This is also accomplished as a result of the persistence characteristics of the oscilloscope phosphor or the sensitivity of the photographic film The echocardiograph thereby converts a succession of relatively irregular amplitudes of the stream of echoes into an esthetically pleasing smooth tracing This signal averaging suppresses information on brief episodes such as would occur on the sudden closing and reopening of valve leaflets Looking at even thousands of such echocardiograms cannot reveal evidence of sudden movements of the valve leaflets during a transitory closure since the recording system eliminates this evidence

Sound recordings pressure recordings and angiocardiography Recent reports of simultaneously recorded sounds pressures and cineangiograms are cited by Tavel and Feigenbaum as evidence against the concept of the closing snap Ross and Criley s paper[2] on the origin of cardiovascular physical signs deals only briefly with the snap The drawings based on cineangiograms are not suitable for analysis of the question More pertinent are the data presented by Thompson and associates[7] whose pressure and sound correlates of the mitral valve are similar to ours except that their apparatus divides the pressure signal arbitrarily at 40 Hz The lower frequencies form a relatively smooth pressure wave while the higher frequencies are separated as the sound waves The recorded simultaneity of the snap with the notch on the atrial y descent and with the sudden acceleration of the rate of fall of ventricular pressure (Thompson s Fig *12*)[7] is strong hydrodynamic evidence that the snap is produced at the instant when blood streaming through the mitral orifice is suddenly stopped by closing of the valve These simultaneous events can in no way represent *opening* of the valve at the instant of the snap as Thompson and co workers[7] and Tavel and Feigenbaum suggest Only the sudden closing of the valve leaflets will generate these physical phenomena

Cineangiograms in Thompson s publication[7] do not provide satisfying evidence that no contrast material enters the left ventricle prior to the snap The silent hiatus of 15 msec between successive frames even at 60 angiographic frames per second impinges on the time domain in which information is sought The picture is further complicated by the cineangiographic injections at very high pressures of materials of high density and viscosity procedures that commonly produce myocardial disturbances for several beats Ambiguities introduced in the publication of frames obtained by these methods may have contributed to difficulties in identifying the discrete published frame in which atrioventricular flow is said to have been initiated (Thompson[7] Figs *9* and *11* and personal communication)

Tavel and Feigenbaum ask whether we believe that aortic ejection clicks and murmurs are also due to momentary valve closure This has been our position for many years Our hydrodynamic studies of the past two decades support the concept that the same physical principle that accounts for the mitral closing snap also generates aortic clicks and ejection murmurs[8,9]

The foregoing analysis and the reasons expressed in detail in our manuscript reaffirm our conclusion that powerful hydrodynamic forces push the leaflets together and momentarily stop the previously moving stream thereby generating the mitral closing snap

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Anticoagulants in pregnancy

To the Editor

The interesting editorial of Hirsh Cade and Gallus (Am Heart J 83 301 1972) on the subject of the role of anticoagulants in pregnancy has prompted me to review some of my early experiments on pregnant dogs which had been given Dicumarol during their last four days of gestation[1] In one instance a litter of seven pups had a prothrombin time of about 200 seconds and the mother had a time of 21 seconds The three pups that were given a water soluble vitamin K (Synkayvite) on their first day survived and their prothrombin time became normal in a week The four untreated pups died of spontaneous internal hemorrhage After 25 years it is now possible to offer an explanation for these observation

Three basic concepts have to be considered (1) Vitamin K is a growth vitamin needed also in the maintenance and repair of tissues (2) Dicumarol

is an antagonist of vitamin K and depresses its metabolic function and (3) in both vitamin K deficiency and after Dicumarol the synthesis of prothrombin, factors VII IX and X is depressed. Factor VII is diminished most and its diminution causes a faulty tissue maintenance which is the major cause of the spontaneous bleeding. The vitamin K requirement of the pup is many times greater than that of the adult dog.[2] When therefore the vitamin K dependent synthetic enzyme is depressed the production of factor VII is no longer adequate to meet the requirement of tissue maintenance and hence the severe and spontaneous hemorrhage.

The only method which measures factor VII deficiency is the one stage prothrombin time and thus this is the only means to diagnose the hemostatic defect caused by anticoagulants. Factor VII is not required in the intrinsic blood coagulation system and therefore all other clotting tests are normal even in a severe deficiency of this factor. Factor VII is a co-factor of tissue thromboplastin and not a true coagulation factor hence former designations such as stable factor and proconvertin are no longer justified.

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Digitalis intoxication

To the Editor

I have read with interest the editorial "Noncardiac symptoms of digitalis intoxication" by V H Lely and C H J van Enter[1] which appeared in the February 1972 issue of the JOURNAL (83 149 1972)

In the VII Central American Congress of Medicine held here in Tegucigalpa in December 1967 we reported the high incidence of visual disturbances in digitalis intoxication. In a prospective study[2] we observed 34 cases in which there were 23 cases showing color vision a 67 per cent incidence. This is not as high as the 95 per cent rate reported by Drs Lely and van Enter but certainly it is indicative of the high incidence of this cardiac manifestation in digitalis intoxication.

Other studies have shown a lower incidence of visual disturbances.[3,4] It is my impression that chromatopsia is a very early manifestation of digitalis toxicity. *It is our experience that when properly* investigated color vision is found as one of the initial symptoms of digitalis intoxication. Yellow vision (xanthopsia) was present as the most common visual abnormality in our study.

The presence of visual disturbances should be investigated in patients taking digitalis as this is an early symptom of digitalis toxicity. This is particularly true in older patients who are apparently more prone to suffer this disturbance.

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going difficulties by dropping the deviant signals. In oscilloscopic display selective filtration[8] smoothes the returning signal. This is also accomplished as a result of the persistence characteristics of the oscilloscope phosphor, or the sensitivity of the photographic film. The echocardiograph thereby converts a succession of relatively irregular amplitudes of the stream of echoes into an esthetically pleasing smooth tracing. This signal averaging suppresses information on brief episodes such as would occur on the sudden closing and reopening of valve leaflets. Looking at even thousands of such echocardiograms cannot reveal evidence of sudden movements of the valve leaflets during a transitory closure since the recording system eliminates this evidence.

Sound recordings, pressure recordings and angiocardiography. Recent reports of simultaneously recorded sounds, pressures, and cineangiograms are cited by Tavel and Feigenbaum as evidence against the concept of the closing snap. Ross and Criley's paper[2] on the origin of cardiovascular physical signs deals only briefly with the snap. The drawings based on cineangiograms are not suitable for analysis of the question. More pertinent are the data presented by Thompson and associates,[7] whose pressure and sound correlates of the mitral valve are similar to ours, except that their apparatus divides the pressure signal arbitrarily at 40 Hz. The lower frequencies form a relatively smooth "pressure" wave while the higher frequencies are separated as the "sound" waves. The recorded simultaneity of the snap with the notch on the atrial y descent and with the sudden acceleration of the rate of fall of ventricular pressure (Thompson's Fig. 12)[7] is strong hydrodynamic evidence that the snap is produced at the instant when blood streaming through the mitral orifice is suddenly stopped by closing of the valve. These simultaneous events can in no way represent *opening* of the valve at the instant of the snap as Thompson and co-workers[7] and Tavel and Feigenbaum suggest. Only the sudden closing of the valve leaflets will generate these physical phenomena.

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Tavel and Feigenbaum ask whether we believe that aortic ejection clicks and murmurs are also due to momentary valve closure. This has been our position for many years. Our hydrodynamic studies of the past two decades support the concept that the same physical principle that accounts for the mitral closing snap also generates aortic clicks and ejection murmurs.[8,9]

The foregoing analysis and the reasons expressed in detail in our manuscript reaffirm our conclusion that powerful hydrodynamic forces push the leaflets together and momentarily stop the previously moving stream, thereby generating the mitral closing snap.

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Three basic concepts have to be considered: (1) Vitamin K is a growth vitamin needed also in the maintenance and repair of tissues. (2) Dicumarol

Books received

Clinical Pharmacology—Basic Principles in Therapeutics Edited by Kenneth L. Melmon M D and Howard F Morrelli M D New York 1972 The Macmillan Company 718 pages Price $16 00 (Also available in paperback at $11 95)

Coronary Heart Disease—A New Zealand Report A report to the National Heart Foundation of New Zealand 1971 from a committee convened by the Scientific Committee of the Foundation The National Heart Foundation of New Zealand 1971 ??9 pages

Management of Arterial Occlusive Disease. Edited by W Andrew Dale M D Based on a conference held at Nashville Tennessee sponsored by the Vanderbilt University School of Medicine St. Thomas Hospital Baptist Hospital and Johnson & Johnson Chicago 1971 Year Book Medical Publishers Inc 506 pages. Price $25 00

Medical Records Medical Education and Patient Care By Lawrence L Weed M D Chicago 1971 The Press of Case Western Reserve University distributed by Year Book Medical Publishers Inc 297 pages.

Missbildungen des Arteriellen Herzendes Morphologie und Morphogenese (Malformations of the Arterial End of the Heart. Morphology and Morphogenesis) By Hans Bankl Munchen Berlin and Wien, 1971 Urban & Schwarzenberg 135 pages.

Missbildungen des Herzens und der Grossen Gefasse By Karl Bock Heinz Tenckmann Martin Herbst, and Ferdinand Spreer Berlin 1971 VEB Verlag Volk und Gesundheit 586 pages

Blood Microrheology—Viscosity Factors in Blood Flow Ischemia and Thrombosis By Leopold Dintenfass Ph D M Sc F R A C I M I E Aust Toronto 1971 Butterworth & Co Ltd 445 pages Price $19 25

Cardiac Surgery 2 Cardiovascular Clinic Vol 3 No 3 Guest Editor Dwight F Harken M D Philadelphia 1971 F A Davis Company 184 pages. Price $12 00

Clinical Phonocardiography and External Pulse Recording Ed 2 By Morton E Tavel M D Chicago 1972 Year Book Medical Publishers Inc 32? pages.

From Cardiac Catheterization Data to Hemodynamic Parameters By Sing San Yang M D L G Bentivoglio M D M S Vladir Maranhao M D and Harry Goldberg M D Philadelphia 1972 F A Davis Company 307 pages. Price $12 00

Postoperative Cardiac Intensive Care. Ed 2 By M V Braimbridge M A M B B Chir F R C S Oxford London and Edinburgh 1972 Blackwell Scientific Publications (distributed in the U S A by F A Davis Company Philadelphia) 176 pages Price $9 00

Symposium on Cardiomyopathy (Pamphlet) Reprinted from *Circulation* November 1971 Vol XLIV No 5 New York 1972 American Heart Association Inc 33 pages. Price $1 00

Therapy in Acute Coronary Care. By Barry B White M D Chicago 1971 Year Book Medical Publishers Inc 156 pages Price $10 95

Traumatic Injuries of the Heart and Great Vessels By Panagiotis N Symbas M D Springfield 1972 Charles C Thomas Publisher 188 pages Price $14 00

Announcements

Czechoslovakian Surgical Congress

The J E Purkyně Czechoslovakia Medical Society will sponsor an international Czechoslovakian Surgical Congress to be held in Bratislava Czechoslovakia on July 13 and 14 1973 Topics to be treated will be surgery of acute and chronic pancreatitis polytraumatism and its life-endangering consequences angiosurgery and various other related subjects

Persons desiring further information should contact The Secretariat, Congress Office Slovak Medical Society Bratislava Mickiewiczova 18 Czechoslovakia.

Jane Nugent Cochems Competition

The University of Colorado School of Medicine announces the Eleventh Annual Cochems Competition funds for which were provided in the will of the late Mrs. Jane Nugent Cochems A prize of $2,500 will be awarded to the author of the best paper in the field of Thrombophlebitis and Basic Vascular

Book reviews

GOLDEN'S DIAGNOSTIC RADIOLOGY Section 18 SELECTIVE ANGIOGRAPHY Laurence L Robbins Editor William N Hanafee Section Editor The Williams & Wilkins Company Baltimore 1972 332 pp Price $25 00

The 18th section of the Golden Series on Diagnostic Radiology is devoted to the use of angiology to outline the circulation to specific organs and areas of the body This field of medicine is developing rapidly and new techniques and applications are appearing rapidly This issue of the series is concerned with seven major aspects (1) fundamentals of selective angiography (2) selective angiography of the abdominal viscera (3) coronary angiography (4) head and neck (5) peripheral vascular (6) adrenal and (7) renal These respective applications are carefully and thoroughly discussed The illustrations are extremely good and well selected and the annotated legends and text are concise and clear This is a good book that should interest cardiologists and cardiovascular surgeons as well as radiologists

HANDBOOK OF EXPERIMENTAL PHARMACOLOGY Band XXXI ANTIANGINAL DRUGS Pathophysiological Haemodynamic Methodological Pharmacological Biochemical and Clinical Basis for Their Use in Human Therapeutics By R Charlier New York 1971 Springer Verlag 442 pp Price $48 60

This volume of the Handbook of Experimental Pharmacology dealing with antianginal drugs should interest all cardiologists and practicing physicians The book presents a good summary of coronary atherosclerosis the pathophysiology of angina pectoris the hemodynamic basis of coronary pharmacology testing and action of coronary vasodilators as well as the use and action of supporting drugs such as morphine sedatives vitamins antiarrhythmic agents alcohol and others With over 2 300 references cited and well prepared author and subject indices this is a valuable and useful reference work as well as a book that should be studied We highly recommend this book to everyone interested in the subject

CLINICAL CARDIOLOGY Third Edition By Velva Schrire M Sc Ph D M D (Cape Town) F R C P E F R C P F A C C Harper & Row Publishers New York 1971 658 pp Price $15 00

The publication of this third edition of Clinical Cardiology indicates the excellent reception of the previous editions. Small by comparison to the other editions this book represents the opinions and practices of an outstanding cardiologist who has been a leader in South African cardiology for many years The presentations are clear and simple The book is clinically oriented throughout and is written for the practicing doctor It incorporates the experiences of Dr Schrire and his approach to patients with heart disease All physicians will find this important contribution to practical clinical cardiology to be a valuable book and it will be especially useful for internists and general practitioners

CARDIAC SURGERY 2 CARDIOVASCULAR CLINICS Series Volume 3 Number 3 Albert N Brest M D Editor in chief Dwight E Harken M D Guest Editor F A Davis Company Philadelphia 1971 184 pp Price $12 00

This is the second volume in the Cardiovascular Clinics series devoted to cardiac surgery The reader will find this book to contain good summaries of the present status of the surgical approach to the management of cardiovascular disease A number of problems are discussed among these is a report by Effler on cardiac revascularization an active surgical approach to coronary heart disease Resectional therapy in infarction assisted circulation pacemakers tumors of the heart cardiac trauma cardiac transplantation and the mechanical heart are among the many presentations briefly treated in this volume The Cardiovascular Clinics series continues to be interesting valuable practical and timely This is another good publication in that group

A PRIMER OF ELECTROCARDIOGRAPHY Sixth Edition. By George E Burch M D and Travis Winsor M D Philadelphia 1972 Lea & Febiger Publisher 292 pp Price $7 75

Now in its sixth edition this monograph has become a classic in cardiology Its purpose is to provide the reader with knowledge of electrocardiography beginning with basic principles of electrophysiology leading to intelligent analysis of electrocardiograms and ultimately to clinical applications of the science The presentation is systematic well organized lucid and in spite of being comprehensive is beautifully concise It is a perfect text for the beginner in electrocardiography Even for the individual with experience in the field much can be gained from the book through solidification of knowledge based on well confirmed sound electrophysiologic principles. By design the authors have excluded controversial issues and new and untested concepts. Through this and other means they have provided the opportunity for one of the most favorable reader time to information gained ratios available in print on this subject.

This reviewer could find no significant criticism to direct toward the book It has truly met its purpose as a primer and can be recommended without reservation in that capacity Binding printing and illustrations are excellent and the price is attractive

American Heart Journal

Sept 1972 Volume 84 Number 3

Editorial

The cardiac patient and hemodynamics

Abraham Noordergraaf, Ph.D.
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Clinicians and physiologists interested in the cardiovascular field designed their own instruments and formulated their own theories until perhaps 1940. Thus Einthoven[1] designed his own string galvanometer for the recording of the electrocardiogram, and Forssmann[2] and later Cournand and Ranges[3] demonstrated the safety of placing the catheter tip within or close to the heart for the measurement of blood pressure.

On the theoretical side, the physician Thomas Young, in the Croonian Lecture[4] given in 1809, argued against what he supposed to be an almost universally held belief that contraction of arterial wall muscle was an important factor in pulse wave propagation. In 1850 Weber,[5] a physiologist, took a strong position against those who believed that the pulse appeared in all parts of the body simultaneously.

Leaders of such stature had to take what professional help they could get. Einthoven had for a number of years a physicist by the name of Bergansius in his employment, while Weber consulted with one of his brothers who was trained in mathematics.[6] But it was not until new technologies, such as electronics, became available that the design and construction of new, smaller, more delicate, and more sophisticated instruments developed into a profession whose aim was to accurately measure biomedical quantities for the first time, or at least more reliably than had been possible before. Those accepting this challenge have been trained as physicists or, more frequently, as engineers. The members of this group now look on themselves as medical physicists or as biomedical engineers, and their chief concern is to provide better instruments for clinicians, for physiologists, and for others who work in various areas of the life sciences. The success of many of these instruments, such as the pacemaker and the defibrillator, testifies to the pragmatic abilities of this group. In this same category are those individuals who adapted the computer to problems in the clinical sciences, such as patient monitoring.

Another quite distinct field has attracted investigators who, failing to find fulfillment in instrumentation, decided to look into the biological phenomena themselves. Its subject matter can be classified under the heading of fundamental biomedical engineering or, more properly, under biophysics. One of the areas in which these investigators are concerned has yielded results that are of immediate interest to cardiovascular clinicians and physiologists. The remainder of this article is devoted to these results and to their implications.

Seventy years ago Frank,[7] a physiologist with a practical mind, was seeking a method

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Received for publication June 28, 1971.
Reprint requests to: Dr. Abraham Noordergraaf, Dept. of Biomedical Engineering, The University of Pennsylvania, Philadelphia, Pa. 19104.

Problems Basic vascular problems under consideration in this instance should be concerned with the underlying mechanisms or processes of vascular disease particularly those associated with thrombosis but not necessarily restricted to it

The competition is open to all persons holding the doctorate degree and entries must be received in triplicate including all charts illustration and photographs on or before November 15 1972 For income tax reasons eligibility is limited to those physicians who are subject to U S income tax regulations

No entry blank or application form is required There are no restrictive rules regarding length or format of the manuscript joint authorship or inclusion of such materials as pictures charts figures etc It is not required that the paper include results of original experimental work nor that it be based on personal clinical experience All manuscripts must be typed with double spacing and each copy together with accompanying illustration etc must be submitted in a folder or cover On request the original copy of the manuscript will be returned if accompanied by a stamped addressed envelope Papers will be judged on originality content, clarity and critical value

Inquiries regarding the competition and all manuscripts should be submitted to the Dean School of Medicine University of Colorado Medical Center 4200 E Ninth Ave Denver Colo 80220

that Frank occupied himself with wave transmission studies during the latter part of his impressive career

Recent studies have shown that the windkessel and transmission theories can be reconciled Starting out from a set of equations that govern the motion of a viscous fluid in distensible vessels and taking into account the architecture of the arterial tree it is now possible to understand why the pulse wave velocity has the observed magnitude as well as to know the reason behind the changing shape of pressure and flow pulses as they travel away from the heart In terms of frequency it has become clear why low frequency components travel much faster than high frequency components This last finding is directly related to the old idea underlying the windkessel theory—that all pressure oscillations in the arterial tree occur almost simultaneously For low frequencies this may indeed be stated with a fair degree of accuracy for higher frequency components it is not true at all For high frequency components of the pulse the arterial tree in its relation to the ventricle approximates the behavior of a distensible tube free of reflection Therefore both the old windkessel theory and the single elastic tube theory (with or without reflection at the distal end of the tube) emerge as only special instances of a more general wave transmission theory in which the architecture of the arterial tree is a key element[4]

This development has significance in several ways It not only increases our understanding of the events in the systemic arterial tree but it also points the way to the solution of important practical problems A few of these deserve mention here

Recent developments

In the past a great deal of effort has been devoted to the experimental determination of the pulse wave velocity in patients for the purpose of evaluating the compliance of the larger arteries The results usually suffered from a high variability On the basis of the recent research summarized above it would seem that meaningful data on the actual phase velocity can be secured only from the fast components of the pressure pulse the speed of the slow components is very sensitive to wave reflection and therefore to the value of the peripheral resistance A pulse wave velocity derived from such components of larger amplitude leads necessarily to an apparent wave velocity which is consequently not a measure of the wall properties alone

The research that led to the present level of our understanding of the events in the systemic arterial tree was much aided by the utilization of very elaborate simulation schemes These are in fact too large to permit convenient programming on contemporary computers[6] Fortunately it appears that in general there is no need for a detailed programming of an entire model If the problem under consideration does not require a detailed knowledge of the local pulse wave velocity in each of the larger arteries the program can be reduced substantially and in a logical fashion without significant loss of accuracy[10] The extent of the reduction depends on the questions posed In most cases handling of the model is within reach of standard analog and digital computers As a result a wider community of investigators will be able to utilize better models of the arterial trees in their own physiological or clinical work in arterial problems than were available in the past

In the event that one wishes to formulate only the properties of the arterial tree in its relation to the left ventricle the solution is even simpler One can deduce logically that the input impedance of the systemic arterial tree can with a good approximation be represented by a series combination of the characteristic impedance of the proximal part of the aorta and the old windkessel approach Therefore this model (called the *westkessel*[10]) contains only three elements each of which has a clear cut physiological meaning By virtue of its simplicity it can be programmed easily on any type of computer or it can be cast in hydraulic form This has direct implications for the solution of intricate problems For as long as physiologists and clinicians have interested themselves in the performance of the heart as a pump the ventricle s

which would enable him to assess the quality of the heart as a pump. He selected left ventricular stroke volume as the best parameter to characterize cardiac performance and developed the "windkessel theory" (originally proposed by Stephen Hales) to provide a basis for his formulations. This theory conceives of the aorta and its many branches as an elastic reservoir with a large outflow resistance. The heart pumps into this reservoir in an intermittent fashion, causing the pressure to oscillate. Frank proposed a way to derive the stroke volume from this pressure, which was required by a noninvasive technique. The approach had wide appeal and during the first several decades of the twentieth century Frank's school produced an abundance of variations on his original windkessel theory, each variation leading to a different formula for estimating stroke volume. Many publications, almost exclusively in German, resulted.

When Frank's school was at the peak of its fame, studies of wave transmission through arteries initiated much earlier by Euler were resumed by Witzig,[8] who proved himself a master in the field. At first ignored by most physiologists and clinicians, these studies were pursued and came to prominence in the period after World War II when interest in the windkessel theory waned. Wave transmission theory deals with pulse wave velocity, wave attenuation, and wave reflection in an arterial tree; hence it is mathematically oriented.

Although Ernst H. Weber had no difficulty in recognizing both windkessel and wave transmission effects in the systemic arterial tree, the attitudes of the advocates of the two theories became rather hostile. The proponents of the windkessel theory argued that the transmission theory, though perhaps more sophisticated, was useless to the clinician, and the transmission people countered by declaring that the confusing variety of stroke volume formulas gave poor results because they were based on an overly simplified concept of the arterial tree. Unquestionably, there was much truth in what each party had to say about the other.

The need for repeated estimates of the state of cardiac function in intensive care units has brought this unsatisfactory state of affairs into sharp focus, especially since the number of these units is increasing rapidly. It is obvious that in many severe clinical conditions the common clinical tests (pulse rate, systolic and diastolic blood pressures, ECG, and VCG) do not provide the information necessary for a rational selection of therapeutic measures and for the judgment of their effects. To meet this need it has been considered mandatory to view the behavior of the circulation as a system rather than just look at stimulus conduction; continuous or semicontinuous monitoring of quantities providing information about fluid dynamics is what is required.

Owing to the progress made by those working in the instrumentation field, blood pressure can now be continuously recorded with a high degree of accuracy at virtually any site in the cardiovascular system. But knowledge of blood pressure itself does not reveal either cardiac output or stroke volume if flow impedance is unknown. It is at this point that major difficulties are encountered, since the instrumentalists have not yet produced a flowmeter suitable for the monitoring of flow in the seriously ill patient.

The clinician needs a way of obtaining flow data on a continuous or semicontinuous basis. In their efforts to solve this problem, it is interesting to note that investigators are rediscovering the approaches that rest on the old windkessel theory. However, the incisive criticisms directed against this theory still apply.[9]

It was once suspected that the wave transmission theory had little if anything to offer which would permit or improve estimates of stroke volume in the clinic, but this cannot be sustained today. Intensive studies of the wave transmission properties of the human systemic arterial tree have brought out what Weber sensed but could not formulate quantitatively: that some aspects of the observed pressure changes are related to the windkessel and others to pulse propagation. If it is true that both aspects are real, it should be possible to interpret them on the basis of a single more general theory. It is of interest to note

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"load," which obviously affects the time course of the myocardial contraction process,[11] has had a puzzling identity It has been variously taken as the value of the peripheral resistance, the arterial pressure operating as counterpressure (in the standard heart lung preparation, one is varied to control the other[1]), the inertia of the blood in the central aorta the compliance of the aorta, and other quantities as well The reason for this is obvious enough, in the past it has been difficult, if not impossible to describe quantitatively what the ventricle "senses," particularly when one wants to study the transient effects during a single systole Clearly, all of the above quantities play a role The westkessel model may well offer a way out of this entangled issue by providing a first step in unraveling the significance of the several factors involved This model not only presents the ventricle with the appropriate input impedance but also with the proper counterpressure

This particular three element representation of the input impedance, valid for the frequency range being studied (including zero frequency where the input impedance is virtually equal to the peripheral resistance) is of immediate interest for a different reason It would permit semicontinuous stroke volume determination in the intensive care unit For this application three elements are required recorded root aortic pressure the westkessel model and any small computer capable of solving for changes in stroke volume in a semicontinuous fashion The values of the elements that make up the model proceed from adjustment for zero flow during diastole, while a single measurement of cardiac output by another technique would provide for absolute values of stroke volume and peripheral resistance Without the latter, changes in stroke volume should be readily identifiable It may be interesting to note here that many of the old windkessel based formulas for stroke volume contain the first element of the westkessel model the aorta's characteristic impedance This has in fact been argued to be the only valuable part of such formulas[12]

This line of thought holds an additional promise By virtue of the way it is constituted, the contour of the ejection curve itself is recorded, not just the curve's time integral, the stroke volume. Evidence that the shape of this curve reflects the contractile properties of the ventricle has been repeatedly presented in the literature

Summary

Frank's windkessel model, as well as the single elastic tube model, have proved to be special cases of a wave transmission theory which is based on equations governing the motion of a viscous fluid in an arborized system of distensible tubes The applicability of the windkessel theory proves to be restricted to the lowest frequencies of interest, which is why windkessel based formulas for stroke volume determination have been unsatisfactory A new approach with a solid foundation in hemodynamic theory is needed to fill the recognized need for evaluation of the left ventricle as a pump Surely problem solving in a real world should rely on our deepened insight into the properties of the cardiovascular system and not on ideas that belong to days gone by, that have long been in need of revision The more general theory advanced here offers such solutions, some of which are outlined in some detail

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Table I Valvular tissues excised and reviewed 1962–1971

Tissues	No	Men	Women
Aortic valve only	137	112 (82%)	25 (18%)
Mitral valve only	183	62 (34%)	121 (66%)
Tricuspid valve only	5	3	2
Aortic and mitral valves	13	6	7
Mitral and tricuspid valves	6	3	3
Total	344	186 (54%)	158 (46%)

fixed in cacodylate buffered 2 5 per cent glutaraldehyde (pH 7 2) for one to two hours After rinsing in buffer the pieces were post fixed for one hour in 1 per cent cacodylate buffered OsO_4 dehydrated rapidly in graded acetone and embedded in Vestopal W One micron sections stained with toluidine blue were used for the selection of representative areas Sections were then cut with glass knives on LKB Ultrotome III They were double stained with uranyl acetate and lead citrate and examined in a Hitachi 8S electron microscope at an electron optical magnification of from X16 000 to X108 000 The micrographs were enlarged photographically as needed

The charts and office records of all patients in whom severe myxoid degenerative changes had been demonstrated were reviewed for the preoperative and cardiac catheterization diagnosis evidence by history or physical examination of rheumatic fever Marfan s disease or arachnodactyly the operative and postoperative diagnosis and the results of the surgical treatment The clinical and pathologic data were then correlated

Results

The case material is summarized in Table I The 344 cases reviewed include 186 men and 158 women patients The men patients ranged in age from 15 to 78 years and the women ranged from 16 to 74 years The mean age for both sexes was 52 years Men patients constituted over 80 per cent of those undergoing excision of the aortic cusps but they only made up one third of the patients undergoing excision of the mitral leaflets

The microscopic study of the excised valves demonstrated the presence of calcium in 192 cases This does not indicate the actual incidence of calcification because in many instances calcified portions of the excised tissue were not used for microscopic examination The actual incidence as found on review of gross descriptions is higher

Two hundred forty three or 70 per cent of the tissues showed some degree of inflammation In three instances there was a marked or diffuse infiltration by polymorphonuclear leukocytes but in the vast majority of cases there were only few focal collections of lymphocytes This was often seen adjacent to or associated with areas of calcification Aschoff bodies were found in seven cases They were few in number old and inactive Most were characterized by zones of fibrosis and scarring with the presence of few Anitschkow myocytes and lymphocytes Characteristic rheumatic vegetations were not seen Vascularization of the valvular tissues was often prominent and in a number of cases there were distinct delicate papillary projections partially covered by endothelial cells

Table II summarizes the myxoid changes observed They were present in 73 per cent of all cases with equal frequency in aortic and mitral valve tissues Most of the valves showed only minimal or slight changes These were characterized by focal areas of vacuolization and the presence of occasional elongated or stellate cell forms The myxoid changes were classified as severe only if they were extensive This classification was by necessity arbitrary since it was principally based on the extent rather than on the qualitative change observed In most of the cases classified as severe a band like area of myxoid degeneration extended through a central or subendocardial portion

Clinical communications

Myxoid changes in cardiac valves: pathologic, clinical, and ultrastructural studies

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Myxoid or mucinous degenerative changes associated with insufficiency of the aortic or mitral valve have been recently described individually and in small series.[1-11] Some authors feel that the myxoid changes are nonspecific[1,4] or the end result of many factors.[8] Others propose a separate disease process, possibly a forme fruste of Marfan's syndrome.[10,11] In some series the aortic valve was reported to be predominantly or exclusively involved,[1,4,5] whereas in others the mitral valve was more frequently diseased.[2,7,8,10] Because of the clinical significance of this lesion and the questions that have been raised concerning its nature, the frequency, degree, and significance of myxoid degenerative changes were evaluated in a large number of surgically excised cardiac valves, and the pathologic and ultrastructural features were studied.

Materials and methods

Slides from all cases of surgically excised cardiac valves for the period from January 1, 1962, to June 30, 1971, were reviewed. The review was conducted blindly without access to patient identification or clinical data. Of the 365 recorded cases, a preliminary examination excluded 21 for lack of adequate tissue sections. The hematoxylin and eosin stained slides and special stains of the remaining 344 cases were examined. The presence or absence of fibrosis, calcification, inflammation, Aschoff bodies, and myxoid changes was recorded. The changes were graded from 1 to 3+, 1+ representing minimal change, 2+ moderate change, and 3+ severe or disruptive changes.

The gross descriptions of all reports were then reviewed and correlated with the microscopic findings. All cases in which the blind microscopic review had demonstrated severe myxoid changes were singled out and further examined.

Portions of normal valve tissue as well as of a surgically excised valve (B 2391-71) showing gross and microscopic evidence of myxoid change were processed for electron microscopic examination. Immediately after the tissue was obtained, small pieces were

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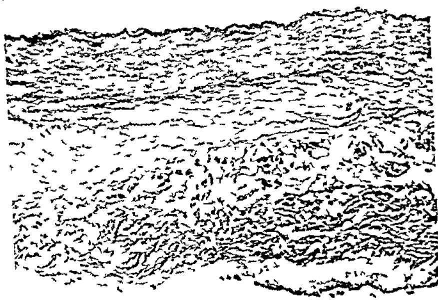


Fig 2 Myxoid degeneration in noncalcified insufficient aortic cusp Case 94 (Hematoxylin and eosin Original magnification X90)

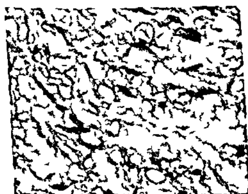


Fig 3 Myxoid changes with prominent vacuolization in aortic cusp adjacent to extensive calcification, Case 29 (Hematoxylin and eosin Original magnification X500)

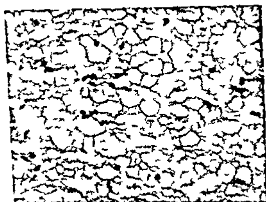


Fig 4 Extensive myxoid changes in insufficient noncalcified mitral valve with elongated chordae Case 202 (Hematoxylin and eosin. Original magnification X500)

Sixteen of these tissues were aortic cusps sixteen were mitral valves and two were tricuspid valves Correlation with the gross descriptions after completion of the microscopic review indicated that in 14 of the 34 cases the valves contained extensive areas of calcification and were grossly considered to be characteristic of chronic rheumatic disease The histologic appearance of the myxoid changes in these cases as exemplified in Figs 1 and 3 is identical with those observed in valve tissue showing myxoid change as the predominant pathologic pattern (Figs 2 and 4)

The 20 cases of severe myxoid change in not significantly calcified presumably nonrheumatic valves are summarized in Table III Some valves were moderately fibrosed but there was no significant scarring or evidence of stenosis and only one (case 61) con

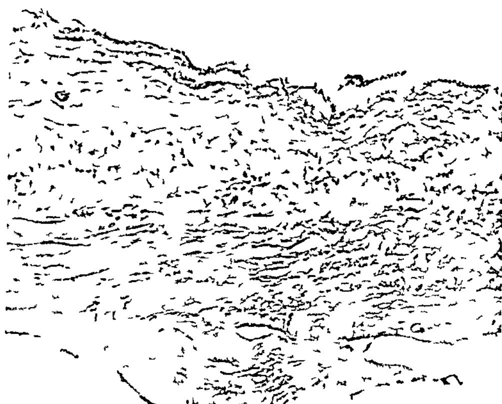


Fig. 1. Myxoid changes in noncalcified portions of aortic cusp tissue from a case (No. 40) of calcific aortic stenosis and insufficiency. (Hematoxylin and eosin. Original magnification ×90.)

Table II. Myxoid changes in excised valve tissues (344 cases)

Tissues	*Minimal slight*	*Moderate*	*Severe*	*Total*
Aortic valves (150)	51	42	16	109 (73%)
Mitral valves (202)	91	39	16	146 (73%)
Tricuspid valves (11)	2	3	2	7
Total	144	84	34	262

of the sectioned leaflet (Figs. 1 and 2) and occupied one third or more of the specimen. High power examination under the light microscope shows the prominent vacuolization (Figs. 3 and 4) with the associated disruption of the normal connective tissue architecture and an apparent relative increase in the ground substance. Alcian blue special stains demonstrate increased amounts of mucopolysaccharides. The histologic changes are quite similar to those observed in the cystic medionecrosis associated with Marfan's disease.

The electron microscopic examination reveals striking changes associated with this myxoid degeneration. The orderly pattern of fibrils in normal valve tissue is shown in Figures 5 and 7. The collagen fibrils are arranged in the form of small bundles in an orderly parallel pattern and the characteristic cross banding is well demonstrated. In contrast, in valve tissue that undergoes myxoid degenerative change the fibrils occur singly in a disorderly arrangement (Fig. 6) and under higher power (Fig. 8) are seen to vary in length and thickness and are often tapered. Cross bandings are no longer recognizable and the extrafibrillar ground substance is of increased translucency and may be increased in amount. This correlates with the light microscopic appearance and the increase in mucopolysaccharides demonstrated by special stains.

Thirty four of the 344 cases reviewed showed myxoid degenerative changes which were considered to be severe and disruptive

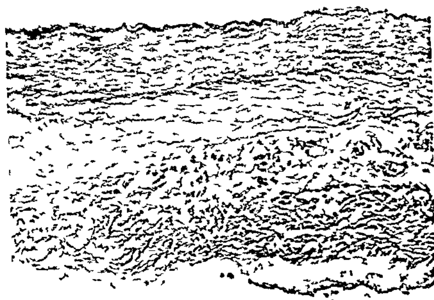


Fig 2 Myxoid degeneration in noncalcified insufficient aortic cusp Case 94 (Hematoxylin and eosin Original magnification ×90)

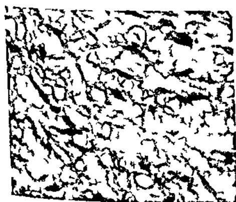


Fig 3 Myxoid changes with prominent vacuolization in aortic cusp adjacent to extensive calcification, Case 29 (Hematoxylin and eosin. Original magnification ×500)

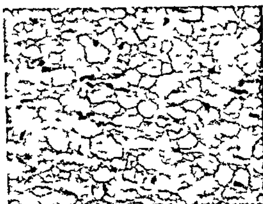


Fig 4 Extensive myxoid changes in insufficient noncalcified mitral valve with elongated chordae Case 207 (Hematoxylin and eosin Original magnification ×500)

Sixteen of these tissues were aortic cusps sixteen were mitral valves and two were tricuspid valves. Correlation with the gross descriptions after completion of the microscopic review indicated that in 14 of the 34 cases the valves contained extensive areas of calcification and were grossly considered to be characteristic of chronic rheumatic disease The histologic appearance of the myxoid changes in these cases as exemplified in Figs 1 and 3 is identical with those observed in valve tissue showing myxoid change as the predominant pathologic pattern (Figs 2 and 4)

The 20 cases of severe myxoid change in not significantly calcified presumably nonrheumatic valves are summarized in Table III Some valves were moderately fibrosed but there was no significant scarring or evidence of stenosis and only one (case 61) con

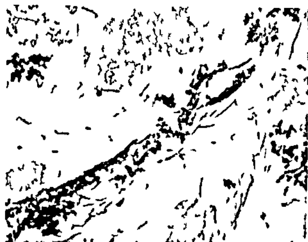


Fig. *5*. Normal mitral valve leaflet. The collagen fibrils are arranged in regular bundles and are embedded in a homogeneous ground substance. (Electron photomicrograph. Original magnification ×16,500.)



Fig. *6*. Myxoid change characterized by a more translucent ground substance and by disruption and disorderly arrangement of collagen fibrils. (Electron photomicrograph. Original magnification ×16,500.)

tained microscopic foci of calcification. The original pathologic gross descriptions were variable but in 12 cases they stressed that the tissue was thin, delicate, flabby, translucent, or edematous. Myxoid changes were described microscopically in 15 of the 20 cases. Such changes were also originally noted in 7 of the 228 cases in which on review they were observed to be present but minimal or moderate in degree.

Sixteen of the patients were men and four were women. They ranged in age from 15 to 68 years with an average age of 42 years. This is approximately ten years younger than the average age for all cases reviewed.

Nineteen of the patients had insufficient

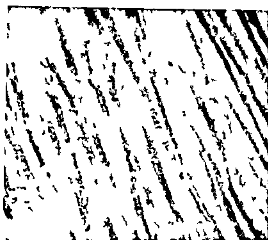


Fig. *7*. High power electron photomicrograph of normal valve tissue showing collagen fibrils with distinct cross bandings in orderly arrangement. (Electron photomicrograph. Original magnification ×108,000.)

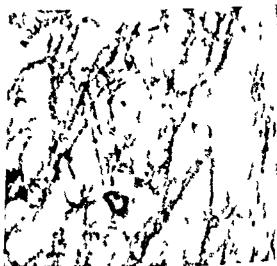


Fig. *8*. Area of myxoid change with fragmentation and haphazard arrangement of collagen fibrils. Cross striations are not demonstrable. (Electron photomicrograph. Original magnification ×108,000.)

valves. One had an atrial septal defect and a cleft mitral valve. In four cases the surgeons found the chordae to be elongated and in one case ruptured. In another instance the chordae were shortened and in this as well as two other cases the surgical impression was that of a rheumatic lesion. Pathologically there was no evidence that this was the case. The postoperative course and follow-up for 15 patients was satisfactory, the follow-up period ranging up to six years. Two of the patients died in the immediate postoperative period and three others died three to five months after surgery, one due to a paravalvular leak

Table III Severe myxoid changes in noncalcified nonrheumatic valves

Patient no	Sex	Age (yrs)	Stigmas of Marfan's disease	Valve excised	Surgical findings	Postoperative condition length of follow-up
59	F	40	No	Aortic	AI postrheumatic	Satisfactory 3 mos
61	M	21	Yes	Aortic	AI dilated annulus (?) SBE	Satisfactory 4 yrs.
89	F	38	No	Mitral	MI elongated chordae	Satisfactory 5 yrs.
94	M	24	No	Aortic	AI bicuspid valve	Satisfactory 1 yr
101	M	15	No	Aortic	AI postrheumatic	Satisfactory 6 yrs.
106	M	52	No	Mitral	MI elongated chordae (?) SBE	Satisfactory 2 yrs.
114	M	51	No	Aortic	AI bicuspid valve	Died postoperatively
116	M	25	No	Tricuspid	TI dilated annulus severe pulmonary hypertension	Died postoperatively
148	M	27	No	Aortic	AI bicuspid valve	Satisfactory 2 yrs.
150	M	57	No	Tricuspid	TI dilated annulus	Satisfactory 2 yrs.
169	M	38	No	Aortic	AI postrheumatic	Satisfactory 5 yrs
177	M	53	No	Aortic	AI SBE	Satisfactory 9 mos
185	F	59	No	Mitral	MI ruptured chordae	Satisfactory 3 yrs
192	F	68	No	Aortic	AI dilated annulus loss of valve substance	Satisfactory 2 yrs
196	M	60	No	Mitral	MI elongated chordae (?) Marfan's	Satisfactory 3 yr
202	M	49	No	Mitral	MI elongated chordae	Satisfactory died 5 mos postoperatively
204	M	27	No	Mitral	MI ostium primum repaired 2 years before	Satisfactory died 4 mos paravalvular leak
221	M	54	No	Mitral	MI postrheumatic	Satisfactory 3 yrs
265	M	50	Yes	Aortic	AI Marfan's	Satisfactory died 3 mos postoperatively
336	M	25	No	Aortic	AI dilated annulus	Satisfactory 1 yr

Abbreviations AI = aortic insufficiency SBE = subacute bacterial endocarditis MI = mitral insufficiency TI = tricuspid insufficiency

Two of the patients both men 21 and 50 years of age had aortic insufficiencies and clinical stigmas of Marfan's disease In the remaining 18 patients there was no historical or clinical evidence of Marfan's disease or habitus

Discussion

The findings reported in this study are based on a microscopic review of a larger number of consecutive surgically excised valve tissues than previously recorded in the literature They illustrate that myxoid changes are a very common finding and are present at least to a slight degree in over two thirds of the cases examined It is obvious that in most cases they do not represent a specific disease process Pomerance and Whitney[13] also called attention to the frequency of these changes as incidental autopsy findings They point out that these changes are the only clinically significant degenerative changes of valves and that chronic valve disease associated with such changes is the commonest cause of heart failure in dogs Myxoid degeneration on the other hand was not seen in the heart valves of aging rats[12] The incidence of severe or disruptive myxoid changes in 10 per cent of our surgical pathologic material corresponds to the findings of Frable[4] who found similar lesions in 23 of 140 excised valves Seven cases were true floppy valves All of his cases occurred in men and involved aortic cusps Our findings demonstrate that severe myxoid changes occur in mitral and tricuspid as well as in aortic valve tissue and in many of these cases they appear to be principally responsible for the valve insufficiency In the mitral valve this may be associated with elongation of chordae It is interesting to note that 5 of the 14 cases which were excluded from the principal study group because the

gross pathologic changes were characteristic of rheumatic disease also had elongated or ruptured chordae tendineae.

Subacute bacterial endocarditis was present or suspected in three of our cases, which fact is of interest since a predisposition to bacterial endocarditis has been previously reported.[8]

Table I shows a striking preponderance of men among patients undergoing aortic valve surgery. This is undoubtedly due to the higher incidence of calcific aortic stenosis and suggests that many of these cases are nonrheumatic. Females predominate in a ratio of two to one in the mitral valvectomy group. Most of the excised mitral valves show morphologic changes characteristic of rheumatic disease, possibly reflecting a slightly greater prevalence of rheumatic fever in females. Our review confirms that severe and clinically significant myxoid changes occur more frequently in men than in women (see Table III). This correlates with a greater number of involved aortic rather than involved mitral valves and may be related to the striking sex distribution of valvular disease in our surgical case material.

The demonstration that myxoid degeneration may occur alone as the principal pathologic change but that histologically identical changes may be associated with chronic rheumatic valvulitis is of particular interest. *The similarity of the observed* changes to those of cystic medionecrosis is striking and has been repeatedly noted.[5, 9, 10, 14] Several patients in other reported series had Marfan's disease[1, 3, 5, 10] and the inclusion of two patients with clinical findings of Marfan's disease in our series further suggests such an association. But even the severe myxoid changes associated with Marfan's disease cannot be distinguished objectively from equally severe changes that occur in chronic rheumatic valvulitis and presumably in other conditions. It does not therefore appear justifiable to consider all cases of extensive myxoid change as a variant of Marfan's disease. Despite statements in the literature that histologic examination of excised valve tissue is rarely helpful,[15] careful routinely performed microscopic studies must be correlated with clinical, surgical, and gross findings in order to recognize those cases in which severe myxoid change is unassociated with rheumatic or with other significant *valvular disease and in* which it has caused valvular insufficiency. These cases then can be recognized as being idiopathic. Some will be found associated with characteristic Marfan's disease whereas the majority are isolated lesions and may be considered a forme fruste of the same syndrome.[11] In view of the great frequency with which myxoid changes are being encountered, we concur with Pomerance and Whitney that at least the less severe changes are a tissue reaction which, like endocardial fibroelastic thickening, is the end result of many etiologic factors including both congenital and aging changes.[8] That aging is probably not very important is indicated by the relatively low average age of 42 years for our group of patients.

The ultrastructural pattern of valve tissue undergoing myxoid change is of particular interest. Normal subendothelial valve tissue consists of fibrocytes, histiocytes and collagenous fibrils embedded in ground substance.[16] The normal amorphous ground substance is optically *homogeneous* and since it consists largely of protein polysaccharides it stains metachromatically.[17] The prominent metachromatic staining of myxoid lesions appears to indicate a relative increase of polysaccharides in the ground substance.[3, 5, 9, 10] This corresponds with the light microscopic appearance of prominent vacuoles (Figs. 3 and 4). However, it appears on examination of the electron photomicrographs that the ground substance is altered and loosened as well as possibly slightly increased in amount. The most striking change is the disorganization and degeneration of the fibrillar structures with loss of cross bandings. It is considered likely that this tissue breakdown and derangement are associated with qualitative changes in the ground substance that lead to changes in staining characteristics.

Summary

The histologic review of 344 consecutive surgically excised aortic, mitral and tricuspid valves demonstrated myxoid degenerative changes in 262 cases. In most cases these changes were minimal but in 34 instances they were severe or disruptive

In 14 instances this was associated with rheumatic valvulitis with marked calcification whereas in 20 cases the myxoid changes were the predominant finding Sixteen of these 20 patients were men and four were women The average age was 42 years ten years less than that of all cases reviewed Eleven aortic seven mitral and two tricuspid valves were involved All were insufficient The histologic findings were consistent with Marfan s disease Two of the 20 patients showed clinical stigmas of th s syndrome The clinical surgical and morphologic correlation suggests that the lesion in this group of patients represents an idiopathic disease process but the morphology alone is nonspecific Particularly lesser degrees of myxoid change appear to be a tissue reaction to a variety of etiologic factors The ultrastructural appearance is characterized by a disruption of the fibrillar pattern qualitative changes with loss of cross bandings in collagen fibrils and a relative increase and greater translucency of the ground substance

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Vectorcardiographic and electrocardiographic differentiation between cor pulmonale and anterior wall myocardial infarction

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The vectorcardiographic differentiation between anterior myocardial infarction (MI) and chronic obstructive pulmonary (lung) disease (COLD) has long been recognized as a difficult diagnostic problem in that both conditions are characterized by reduced or absent anteriorly directed initial forces It is surprising, therefore that only one quantitative investigation with the purpose of improving the differentiation has been reported by Ishikawa and associates[1] In their sample of 1 002 patients with myocardial infarction (MI) and 405 patients with pulmonary emphysema (PE) over 300 vectorial and scalar (Frank leads X Y and Z) items were measured with the aid of electronic computers A significant improvement in the separation of these two conditions was achieved when multivariate statistical analysis including multidimensional (arithmetic) vectors was utilized By means of a combination of a relatively small number of items which could be measured manually the original 50 per cent of emphysema records which could have been erroneously interpreted as MI was reduced to 16 per cent More complex multivariate analysis with a larger number of items resulted in further improvement with a residual error of 13 per cent

In view of the relatively limited information available we felt that another quantitative investigation of this important problem would be justified Our sample of MI and COLD patients is smaller than that of the Ishikawa group However, the selection of MI patients was based on detailed autopsy analysis and the localization of MI is more precise Ishikawa and co workers used only the Frank leads We used Frank leads as well as the conventional lead electrocardiogram (ECG) so that the diagnostic performance of the two lead systems could be compared The number of items analyzed, being limited to those which could be measured manually, was much smaller than in Ishikawa's study

Materials and method

The sample consisted of 52 patients with COLD (age range 42 to 79 years mean age 56 0) and 35 with anterior myocardial infarction (MI) (age range 35 to 78 years

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Table I

Scalar and vectorial items analyzed—Frank leads	
Scalar X Y Z lead Q R S T	12 items
Vectors X Y Z coordinate of QRS 20 msec 25 msec max −20 msec and maximal T	15 items
Combination Rx + Rz Sx/(Sx + Rx) Qz/(Qz + Rz) Sx + Qz	4 items
Time interval Qx Qy Qz QRS and peak time	5 items
Total	36 items
Items analyzed in 9 lead ECG (standard leads V₁ V₆)	
Q R S amplitude in 9 leads	27 items
P amplitude in Leads I II III and aVF	4 items
Q duration in 9 leads	9 items
S/R, Q/R in 9 lead	18 items
Peak-to-peak QRS amplitude in 9 leads	9 items
QRS duration, frontal axis RV₆ + SV₁ RV₁ + SV₁	4 items
Total	71 items

mean age 57 5) who had been admitted to Minneapolis Veterans Administration Hospital COLD cases were classified as moderate to severe on the basis of clinical and lungs radiologic findings and pulmonary function tests The 35 cases of infarction were verified by autopsy findings A scar of the myocardium extending at least 2 0 cm in one dimension and/or acute degenerative necrotic changes were taken as criteria for MI Generalized myocardial fibrosis was excluded Post mortem examination of the hearts was performed as previously described[3] Five longitudinal and three transverse sections yielded 15 areas for MI localization Ten patients had pure anterior infarction 11 had anteroseptal and lateral MI 9 had anterior and inferior MI 5 had extensive infarction with an involvement of the anteroseptal inferior and lateral wall

The corrected orthogonal vectorcardiograms (Frank lead system) were recorded with an Electronics for Medicine DR 8 photographic recorder The electrodes were placed at the level of the fourth intercostal space in the supine position The frontal horizontal and left sagittal planar loop projections as well as X Y and Z scalar

Table II Categories of vectorial and scalar items with high correlations within each category and little correlation between the different categories

Spatial	Scalar
(1) 20 msec X	Qx amplitude
25 msec X	Qx amplitude
maximal QRSx	Rx amplitude
−20 msec X	Sx amplitude
maximal Tx	Tx amplitude
−20 msec Y	Sy amplitude
maximal QRSy	Ry amplitude
(2) maximal QRSz	Rz amplitude
maximal Tz	Tz amplitude
(3) 20 msec Z	Qz amplitude
25 msec Z	Qz duration
(4) 20 msec Y	Qy amplitude
25 msec Y	Qy duration
(5) QRS duration	
peak time	

tracings (paper speed 20 cm per second) were analyzed In the upper part of Table I the 36 items measured in the Frank leads are listed and in the lower part the 71 items measured in the conventional nine lead ECG (augmented unipolar leads were not utilized except for P in aV_F)

The general purpose of the statistical analysis was determination of the minimum number of items (single or combinations) for the best separation of MI and COLD As a first step the means and the standard deviations were calculated for each item in both groups (COLD and MI) As a second step to avoid a redundancy of information the correlation coefficients between the 36 Frank lead items were determined in COLD and MI amounting to 630 correlations * and the items with a high correlation coefficient were classified into the same group Then the items were clustered into five independent categories as shown in Table II The correlation among the items in each category is high but there is little correlation between the items of the different categories The Student t test was carried out for the two groups Four items with the highest t value in each category were chosen as parameters for the best discrimination of COLD and anterior MI

*2 450 [illegible] 9 [illegible] nal ECG leads.

Table IIIA. Means and standard deviations (S D) of scalar and vectorial items for COLD and MI patients with statistical significance of differences (t test)—Frank leads

Items		COLD		MI		t
		Mean	S D	Mean	S D	
Max spatial QRS	x	0 037 mv	0 525	0 558	0 6'6	4 20†
	z	0 264	0 365	0 724	0 ,96	3 ?0*
Max spatial T	x	0 063	0 116	−0 014	0 110	3 12*
	y	0 241	0 141	−0 004	0 154	7 66†
20	z	−0 124	0 153	0 160	0 245	6 09†
25	z	−0 087	0 251	0 354	0 353	6 ,,†
Scalar amplitude	Q	0 012 mv	0 045	0 085	0 1?6	3 ?8
x	R	0 362	0 253	0 649	0 462	3 35†
	S	0 285	0 302	0 153	0 150	2 ,1
	T	0 076	0 091	−0 008	0 124	3 64†
y	T	0 192	0 096	0 000	0 1,0	6 0,†
z	R	0 489	0 252	0 994	0 397	6 33†
Rx + Rz		0 851	0 357	1 643	0 681	6 65†
Sx/(Rx + Sx)		0 417	0 287	0 245	0 264	? 82
Qz/(Qz + Rz)		0 313	0 167	0 147	0 162	4 52†
QRS duration		93 56 msec	20 48	105 49	13 92	3 23*
Qx duration		3 17	7 92	12 47	13 45	3 64†
Qz duration		30 19	14 31	14 26	10 09	5 ,0†

*p <0 01
†p <0 001

These four items were selected Rx + Rz 25 msec z QRS duration and Sx/(Sx + Rx) * Finally, the discrimination of the two groups was performed with a 'weighted vector difference' method †[4 5]

The respective distances of each subject from the arithmetic mean vectors of COLD and MI were obtained using a weighting factor inverse to the standard deviation Therefore, the distance corresponded with the probability density of a subject to be classified in COLD or MI

The statistical evaluations of the data were performed by the use of a CDC 3300 computer

Results

I Orthogonal (Frank) leads Table IIIA shows the means and standard deviations (S D) for COLD and MI groups with highly significant mean differences between the two groups (t test)

When grouped according to the correlation coefficient, redundant information was reduced and a small number of effective

*Frank leads.
†See Appendix I for details.

parameters was obtained (see Table IV

In each category the following iten were selected for best discrimination b tween COLD and MI (1) amplitude of wave in Lead X(Rx) (t = 3 35) (2) ampl tude of R wave in Lead Z(Rz) (t = 6 33 (3) Z component of spatial 25 msec vect (25 msec z) (t = 6 77), (4) QRS duratio (t = 3 23)

Since the combination of Rx and R gave a higher t value (6 68) than its ind vidual items Rx + Rz was selected single parameter for the discriminatio Sx/(Rx + Sx) was utilized additionall because of its usefulness in the discrimina tion of COLD patients from normal sub jects[3] Table IV (upper part) shows the best discriminating values with percent age distribution of COLD and MI In the individual use of the above parameters Rx + Rz resulted in 75 per cent of cor rect diagnoses in COLD patients and 83 per cent in MI patients 25 msec z in 81 and 77 per cent respectively and QRS duration in 85 and 57 per cent, respec tively The combination of Rx + Rz and 25 msec z identified correctly 83 per

Table IIIB *Means and standard deviations (S D) of conventional ECG items for COLD and MI patients with statistical significance of differences (t test)*

Items	COLD		MI		t
	Mean	S D	Mean	S D	
RI	0 281	0 156	0 556	0 382	4 66
SV_1	0 499	0 419	1 158	0 941	4 45
SV_2	0 942	0 678	1 643	1 095	3 69
QV_1	0 007	0 031	0 552	1 002	3 93
RV	0 818	0 409	0 457	0 539	4 15
QV_4	0 008	0 027	0 217	0 431	3 50
P_{II}	0 188	0 068	0 126	0 080	3 88
P_{III}	0 145	0 072	0 086	0 076	3 61
PaVF	0 168	0 077	0 103	0 074	3 92
QDV_3	1 10	4 2	23 4	37 0	4 33
QDV_4	0 7	2 8	19 9	31 9	4 33
QDV_5	1 5	4 2	19 7	30 2	4 30
QRSd	83 1	8 6	94 3	8 9	5 87
S/R in V_1	5 1	5 2	14 5	17 9	3 56
V_2	3 6	3 0	17 7	23 8	4 23
V_3	2 5	2 0	11 8	17 0	3 90
V_4	1 1	0 9	5 4	8 9	3 53
Total deflection I	0 397	0 163	0 647	0 375	4 25
V	0 744	0 368	1 530	0 846	5 93
V_2	1 303	0 764	2 272	0 827	5 61
V_3	1 429	0 690	2 217	0 812	4 86
$RV_4 + SV_1$	1 512	0 562	2 307	1 346	3 803
$RV_6 + SV_1$	1 319	0 546	2 363	1 318	5 111

*p <0 001

cent of COLD cases and 88 per cent of MI cases (Table V) The combination of Rx + Rz 25 msec z and QRS duration identified correctly 88 per cent of COLD and 88 per cent of MI cases the addition of Sx/(Rx + Sx) resulted in correct identification of 88 per cent of COLD and 91 per cent of MI cases

As an additional estimative method a linear discriminant function[6] was utilized The coefficients of the four parameters are listed in Table VI (left Frank leads right conventional lead) and the percentage of correct classification was estimated as 89 per cent using Mahalanobis distance (Fig 1) * This result showed approximately the same diagnostic accuracy as the weighted vector difference method

II Conventional leads Table IIIB lists the means and standard deviations of all items with highly significant differences ($p = < 0.001$) between the COLD and MI groups In a procedure similar to the evaluation of the orthogonal Frank leads four items were selected for differentiation between the COLD and MI groups and listed in the lower part of Table IV $RV_6 + SV_1$* (corresponding to Rx + Rz) RV_4 (corresponding to 25 msec z) QRS duration and PaVF

The identification of the COLD group was quite similar for $RV_6 + SV_1$ and Rx + Rz but better for the 25 msec anterior vector coordinate than for RV_4 probably because it is more anteriorly directed The correct identification of 60 per cent by means of PaVF was surprisingly low The correct identification of the MI group ranged from 71 to 77 per cent in the four items

The differentiation between COLD and MI groups by means of combinations of conventional ECG items is listed in the lower part of Table V The correct identification of 81 per cent of COLD patients

*This item was selected because of the directional similarity to Rx + Rz

Table IV Recognition rate of COLD and MI by individual parameters in number and percentage of

Disease	Frank leads			
	Rx + Rz	25 msec	QRS duration	Sx/(Rx + Sx)
COLD (52)	39 (75%)	42 (81%)	44 (85%)	30 (58%)
MI (35)	29 (83%)	27 (77%)	20 (57%)	27 (77%)
Best discriminating value	1 12 mv	0 10 mv	100 7 msec	0 33 mv

Table V Recognition rate by various combinations of parameters

Disease	Frank leads		
	Rx + Rz + 25 msec	Rx + Rz + 25 msec + QRS duration	Rx + Rz + 25 msec + QRS duration + Sx/(Rx + Sx)
COLD (52)	43 (83%)	46 (88%)	46 (88%)
MI (35)	31 (88%)	31 (88%)	32 (91%)

with two combinations $RV_6 + SV_1$ plus QRSd, is quite satisfactory and is not improved by adding other items In contrast the identification of MI patients is improved by adding RV_4 and PaVF to 94 and 97 per cent, respectively and is excellent

The results obtained with using the linear discriminant functions are listed in Table VI, right part

Discussion

There were a considerable number of COLD patients with reduced or absent initial anteriorly directed QRS forces (13 of 52 patients [25%]) As emphasized by Ishikawa and associates[1] these are frequently misdiagnosed as MI in routine clinical vectorcardiography or electrocardiography A reasonably good discrimination using only two parameters, Rx + Rz and "25 msec z," was obtained because as previously noted[8] a reduction in amplitude of Rx and Rz occurred only in cases of COLD The discriminative point of Rx + Rz between MI and COLD of 1 12 mv would indicate a recognition rate of 83 per cent in cases of MI and 75 per cent in instances of COLD respectively However, the Z component of the spatial 25 msec vector (25 msec z) was a still better parameter to differentiate the two disease entities Utilizing 0 10 as a discriminative threshold a correct identification of 81 per cent of cases of COLD and 77 per cent of cases of MI (Table IV) was possible

Many investigators have used the Q amplitude and/or duration or Q/R ratios in lead Z for discrimination although the distribution of the Q amplitude or Q/R ratios was quite different from a normal distribution On the other hand, in our material the distribution of "25 msec z" was a fairly normal distribution and therefore superior for statistical analysis The distribution of 25 msec z was wider and

ent

	Conventional ECG leads			
Disease	$RV_6 + SV_1$	RV_4	QRSd	PaVF
LD (52)	38 (73%)	34 (65%)	44 (85%)	31 (60%)
(35)	27 (74%)	26 (74%)	27 (77%)	25 (71%)
t discriminating value	1 62 mv	0 40 mv	88 1 msec	0 13 mv

	Conventional ECG leads		
Disease	$RV_6 + SV_1$ + QRSd	$RV_6 + SV_1$ + QRSd + RV_4	$RV_6 + SV_1$ + QRSd + RV_4 + PaVF
D (52)	42 (81%)	42 (81%)	40 (79%)
35)	31 (89%)	33 (94%)	34 (97%)

was deviated more posteriorly in cases of MI than in instances of COLD

QRS duration improved the diagnostic separation only slightly because of the overlapping distribution of this parameter in both groups The cut off point was 100 7 msec.

Sx/(Rx + Sx) was one of the best discriminators between COLD and Normal but less effective for discrimination of COLD from MI However in combination with other items it improved only slightly the discrimination (Table IV)

As shown in Table V use of the combination of Rx and Rz QRS duration 25 msec z component and Sx/(Sx + Rx) i e four items easily manually determined resulted in correct identification of 88 per cent of COLD patients and 91 per cent of MI patients which compares favorably with results of the Ishikawa group Comparing the diagnostic performance of orthogonal Frank leads and conventional ECG leads the Frank leads are somewhat superior for correct recognition of COLD patients (88 vs 81 per cent) while the conventional leads are somewhat superior for correct identification of MI (97 vs 91 per cent) The differences however are not very great Examples for clinical application of the weighted vector differences are given in Appendix II It would appear that linear discriminant function analysis significantly improves the differentiation of MI from COLD However there is little difference in reliability between Frank lead and conventional ECG lead analysis

Summary

The vectorcardiographic differentiation between anterior wall myocardial infarction (MI) subjects (35 patients selected from detailed autopsy data) and 52 patients with chronic obstructive lung disease (COLD) was considerably improved by multi variate statistical analysis Thirty six scalar

Table VI Linear discriminant function between COLD and MI*

Frank leads		Conventional ECG leads	
Parameters	Coefficients	Parameters	Coefficients
Rx + Rz	−3 34	$RV_6 + SV_1$	−1 57
25 msec. z	−5 55	RV_6	+3 44
QRS duration	−0 0389	QRSd	−0 116
Sx/(Sx + Rx)	−0 0359	PaVF	+13 4
Constant	+8 82	Constant	+9 03
Mahalanobis distance	5 66	Mahalanobis distance	5 35
L	1 19	L	1 16

*The coefficients are to be multiplied with values of the combined parameters listed in the first column and added If the sum is negative it indicates MI if positive it indicates COLD as illustrated in the scatter diagram of Fig 1

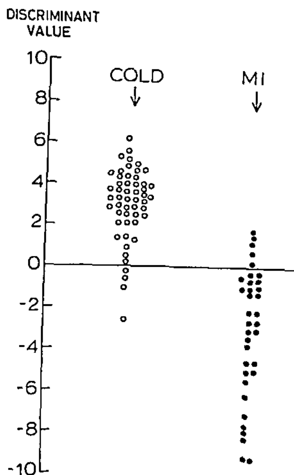


Fig 1 See footnote of Table VI

items, all measured manually were analyzed The combination of only four items Rx + Rz, 25 msec z component QRS duration and Sx/(Sx + Rx) resulted in correct identification of 88 per cent of patients with COLD and 91 per cent of patients with MI Multivariate analysis of conventional ECG items differentiated between the two groups equally well, somewhat superior for MI with correct identification of 97 per cent of cases for combination of four items and somewhat inferior for COLD with correct identification of 81 per cent of instances with a combination of two items ($RV_6 + SV_1$ plus QRS interval)

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Appendix I

Weighted vector differences Let

$$d(p,\mu^A) = \sqrt{\sum_{i=1}^{N} [W_i^A (p_i - \mu_i^A)]^2}$$

$$d(p,\mu^B) = \sqrt{\sum_{i=1}^{N} [W_i^B (p_i - \mu_i^B)]^2}$$

where

p_i = i^{th} component of unclassified point μ_i^A = i^{th} component of mean value from Group A μ_i^B = i^{th} component of mean value from Group B N = number of components W_i^A = weights inversely proportional to the standard deviation of the point p_i in Group A W_i^B = weights inversely proportional to the standard deviation of the point p_i in Group B

We classify $p \epsilon A$ if $d(p,\mu^A) < d(p,\mu^B)$ $p \epsilon B$ if $d(p,\mu^B) < d(p,\mu^A)$

Appendix II

Table A Examples for clinical application of linear discriminant function

Parameters	*Coefficients*
Rx + Rz	−3 344
25 msec. z	−5 546
QRSd	−0 039
Sx/(Sx + Rx)	0 036
Constant	8 824

Example 1

PATIENT NO 1 FROM COLD GROUP
−3 344 × 0 799 − 5 546 × 0 059
−0 039 × 93 0 + 0 036 × 0 565
+8 824 = 2 218

Example 2

PATIENT NO 46 FROM MI GROUP
−3 344 × 1 429 − 5 546 × 0 337
−0 039 × 100 0 + 0 036 × 0 072
+8 824 = −1 723

*Table VI Linear discriminant function between COLD and MI**

Frank leads		Conventional ECG leads	
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QRS duration	−0 0389	QRSd	−0 116
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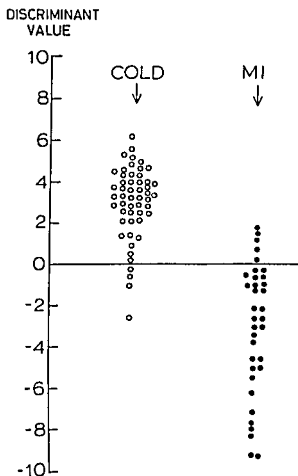


Fig 1 See footnote of Table VI

items, all measured manually were analyzed The combination of only four items Rx + Rz, 25 msec z component, QRS duration and Sx/(Sx + Rx) resulted in correct identification of 88 per cent of patients with COLD and 91 per cent of patients with MI Multivariate analysis of conventional ECG items differentiated between the two groups equally well, somewhat superior for MI with correct identification of 97 per cent of cases for combination of four items, and somewhat inferior for COLD with correct identification of 81 per cent of instances with a combination of two items ($RV_6 + SV_1$ plus QRS interval)

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mal pair recorded a high right atrial (HRA) electrogram In addition a bipolar catheter* was introduced into another antecubital vein and advanced to the right ventricular apex or outflow tract for ventricular pacing During all stimulation sequences the surface electrocardiogram (ECG) electrograms and time lines generated at intervals of 10 and 100 msec were displayed on a multichannel switched beam oscilloscope† and recorded via a universal matching amplifier† onto magnetic tape When the gain of the matching amplifier was adjusted the recording of the His potentials could be enhanced without overloading the tape recording assembly Clipping of the ventricular electrogram resulted from this arrangement Standard ECG Leads I II V_1 and V_6 were simultaneously recorded on a Sanborn 4560 recorder ‡

The refractoriness of various components of the AV conducting system (AVCS) was determined using the extrastimulus method[10 11] The bipolar atrial electrogram was electronically counted utilizing a specially designed digital stimulator § allowing a premature atrial depolarization (A_2) to be introduced at variable intervals after every eighth sinus depolarization (A_1) The stimulus was a cathodal rectangular wave of 1 5 msec duration delivered at 2 to 3 times diastolic threshold The prematurity of the stimulus was progressively decreased by 5 to 10 msec intervals until atrial refractoriness was encountered In three of the seven patients the sequence of premature atrial stimulation was repeated at rates faster than the sinus rate The basic drive following the premature beat was omitted to observe the effect of the premature beat The following definitions were used and their intervals recorded

Atrioventricular conduction system (AVCS) Includes the atrium specialized intra atrial tracts AV node bundle of His the three fascicular divisions of the bundle of His and Purkinje network

Ventricular specialized conducting system (VSCS) A subdivision of the above term which includes the bundle of His and all specialized conducting tissue distal to it

Effective refractory period (ERP) of the AVCS The shortest test $A_1 A_2$ interval at which the premature atrial response still conducts to the ventricle

Effective refractory period (ERP) of the VSCS The shortest interval between two His depolarizations ($H_1 H_2$) at which H_2 still propagates to the ventricle

Functional refractory period (FRP) of the AVCS The minimum interval between two successive ventricular responses both propagated from the atrium ($V_1 V_2$)

Functional refractory period (FRP) of the AV node The shortest $H_1 H_2$ interval between two successive His bundle responses both propagated from the atrium

All equipment was suitably grounded and isolated All patients tolerated the procedure without complications

Results

The refractoriness of the various parts of the AVCS was determined in 50 patients using the extra stimulus method The most common site of block of premature atrial impulses and hence the structure with the longest effective refractory period (ERP) was the AV node However in seven patients block of premature atrial impulses occurred below the bundle of His All were men between the ages of 45 and 66 Patients 1 and 3 had clinical histories of angina pectoris Patient 7 had myotonic dystrophy The remainder were found to have no evidence of heart disease None of the seven was receiving medication prior to the study Table I lists the functional properties of the AVCS in these seven patients In all patients the ERP of the VSCS during sinus rhythm or slow basic cycle length was prolonged as compared to a group of normal subjects These patients were identified at the time of study and further evaluation was performed to determine whether the AMR was located within the ventricular muscle or within the VSCS This was accomplished by connecting the output of the stimulator, using low milliamperage to a pacing catheter located in the right ventricular apex (five

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§ FBN Elect ... cs, Philad lphia, Pa

Localization of an area of maximum refractoriness or "gate" in the ventricular specialized conduction system in man

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The A V node is usually the area demonstrating maximum refractoriness in man and as such might be called a gate However, in approximately 10 per cent of patients (including normal subjects) and almost invariably in patients with LBBB [1] block of premature impulses occurs at some level distal to the bundle of His

Previous experimental studies have shown that action potential duration progressively increases from the bundle of His distally toward the Purkinje fiber network[2,3] and then diminishes in the transition from Purkinje cells to muscle [4-6] Myerburg and associates[7,8] subsequently have demonstrated by microelectrode techniques an area of maximum refractoriness (AMR) or ' gate ' just proximal to the termination of free running Purkinje fibers in muscle at the site of maximum action potential duration

The AMR has not been previously demonstrated in those patients in whom block of premature atrial beats occurs distal to the bundle of His

In the present study an attempt was made to localize this AMR more precisely in the human heart

Methods

Right heart catheterization was performed in the postabsorptive, nonsedated state A signed consent was obtained from all patients Using a tripolar electrode catheter† introduced percutaneously into a femoral vein His bundle recordings were obtained according to methods previously described [9] In addition a quadripolar catheter† was introduced into an antecubital vein and positioned fluoroscopically against the lateral wall of the high right atrium The distal pair of electrodes was used for atrial stimulation while the prox

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†U S Catheter & Instrument Corp Glens Falls, N Y

	A V node							
	FRP	*ERP*	*VSCS ERP*	$H_1 V$	Δ	*Ventricular pacing site*	*Ventricle refractory* ($H_1 V$)	*Atrium refractory* ($A_1 S$)
ı	430	3 0	(520) 470	470	40	Apex	410	360
ł	360	310	360	‡	—	—	—	300
	350	270	345	‡	—	—	—	270
ı	495	470	540	395	145	Outflow	345	390
ı	480	400	480	395	85	Outflow	345	375
	450	310	530	415	115	Outflow	—	290
ł	450	410	460	430	30	Apex	—	390
ı	440	360	440	‡	—	—	—	340
ı	3 0	270	365	335	30	Apex	330	240
	385	345	410	335	75	Apex	325	290
	610	450	680	460	220	Apex	400	220

Δ = Difference between ERP of the VSCS and the H V interval.
A_1S = A measure of atrial refractoriness. The longest interval from preceding atrial impulse at which the stimulus (S) fails to depolarize the atrium.
SCL = Sinus cycle length.
BCL = Basic cycle length (paced).
LAF = Left anterior fascicular (hemi) block.
RBBB = Right bundle branch block.
LBBB = Left bundle branch block.
‡Study limited by atrial refractoriness. No impulse blocked below the bundle of His.

retrograde activation of the bundle of His and atria This indicates that the area(s) of the VSCS which was maximally refractory and thereby prevented antegrade conduction to the ventricles (panel *B* $H_1 H_2$ interval = 515 msec) was less refractory at the time the retrograde ventricular impulse activated this region and consequently could permit retrograde conduction to the bundle of His (panel *C* $H_1 H' =$ 575 msec) This can be explained by the fact that when the ventricles are pre excited ventricular activation initially begins by muscle to-muscle depolarization A few milliseconds later (undetermined) the impulse enters the VSCS This slight delay causes the retrograde impulse to reach the AMR at a time later in the cardiac cycle when it is less refractory This explanation is supported by the fact that the interval from the onset of ventricular depolarization (V_s) to the retrograde His deflection (H) measures 155 msec which exceeds by 85 msec the longest H V interval which was obtained (panel *A* $H_2 V_2 =$ 70 msec) just prior to failure of antegrade conduction to the ventricle (panel *B*)

Fig 3 taken from the same patient demonstrates a phenomenon which might be interpreted as an AMR or gate during retrograde conduction In panel *A* a premature ventricular response (V) is elicited at an $H_1 V$ interval of 420 msec resulting in delayed retrograde activation of the bundle of His and atria There is a fully compensatory pause following the induced ventricular beat. In panel *B* an earlier stimulus at an $H_1 V$ interval of 415 msec fails to conduct retrogradely to the bundle of His resulting in an interpolated ventricular beat The next sinus beat is slightly premature due to the ventriculophasic effect of the interpolated beat The A H interval of the sinus beat shows no effects of retrograde concealed conduction

The results of the findings presented

*Table I Electrophysiological data**

Patient (age)	Cycle length	ECG	A H†	H V	AVCS	
					FRP	ERP
1 I M (55)	BCL = 1 150	LAF −60 QRS = 0 12 sec	100	45	545	380
	BCL = 600		135	45	400	310
	BCL = 500	"	140	45	345	270
2 P H (64)	SCL = 860-1 180	RBBB + LAF −60	110	45	530	465
	BCL = 850		120	45	510	425
3 A M (59)	SCL = 880 920	LAF −60 QRS = 0 12 sec	100	55	555	495
4 J L (66)	SCL = 1 150 1 290	Normal	90	40	545	410
	BCL = 820	"	100	40	460	360
5 D T (60)	BCL = 700	LAF −30	85	45	580	270
6 I E (45)	BCL = 800	Normal	90	50	410	560
7 T M (46)	BCL = 800	LBBB normal axis	125	90	710	720

*All values expressed in milliseconds.
†Abbreviations used
A H = Interval between the atrial electrogram and bundle of His electrogram as recorded by the His bundle catheter
H V = Interval between the His deflection and the earliest evidence of ventricular activity (whether in the His bundle electro ram
the peripheral ECG)
AVCS = (The entire) atrioventricular conduction system
AVN = Atrioventricular node
VSCS = Ventricular specialized conduction system
ERP = Effective refractory period
FRP = Functional refractory period
H_1 V = The shortest interval following depolarization of the bundle of His (during SCL or BCL) at which the ventricle can be effecti
stimulated

patients) or outflow tract (two patients) The latter was deliberately utilized as a pacing site because of the near complete absence of Purkinje network in the outflow tract That the level of block was not at the ventricular muscle level but proximal to this region is indicated by the fact that in each case, regardless of pacing site a ventricular depolarization could be elicited earlier in diastole than the point at which H_2 was blocked Reference to Table I shows that in every instance the H_1 V interval was shorter by a range of 30 to 220 msec than the $H_1 H_2$ interval at which H_2 blocked

Fig 1 (Patient 6) is a representative example In panels *A* to *C*, the right atrium is being paced at a constant cycle length In panel *A*, the prematurely evoked His bundle depolarization (H_2) conducts to the ventricle at an H_1 H interval of 410 msec In panel *B*, a slightly more premature atrial impulse evokes an earlier His bundle depolarization which fails to conduct to the ventricle at an $H_1 H_2$ interval of 400 msec In panel *C* the sequence is identical to that of panel *B* with the added event that the ventricle is being simultaneously stimulated at an $H_1 V_s$ interval of 380 msec These findings indicate that the AMR was located somewhere between the bundle of His and the most distal portion of the Purkinje network

Additional observations were made in two patients (Patients 2 and 3) in whom a retrograde His deflection could be seen during ventricular stimulation In Fig ? (Patient 3) panel *A*, the shortest $H_1 H_2$ interval (530 msec) which still permitted antegrade conduction to the ventricle is shown In panel *B* antegrade conduction fails at an H_1 H interval of 515 msec In panel *C* the same preceding cycle length is present as in panels *A* and *B* The ventricle is prematurely stimulated at an $H_1 V_s$ interval of 430 msec, resulting in

	A V node							
	ERP	FRP	VSCS ERP	H_1V	Δ	Ventricular pacing site	Ventricle refractory (H_1V)	Atrium refractory (A S)
ı	450	3 0	(520) 470	4 0	40	Apex	410	360
ł	360	310	560	‡	—	—	—	300
ı	350	270	345	‡	—	—	—	270
3	495	4 0	540	395	145	Outflow	345	390
	480	400	480	395	85	Outflow	345	375
	450	310	530	415	115	Outflow	—	290
	450	410	460	430	30	Apex	—	390
ı	440	360	440	‡	—	—	—	340
)	550	? 0	365	335	50	Apex	330	?40
	585	345	410	335	75	Apex	3?5	290
	610	450	680	460	220	Apex	400	220

= Difference bet ee ERP of the VSCS and the H_1V int rval.
+S A measure of atrial r f act ness. Th lo ge t interval fr m a precedi g at ial imp lse at whi h the tim lus (S) f ls to depolarize the tri m
CL = Sinu cycl le gth
CL Basic cycle length (paced)
AF Left terior fasci lar (hem) block.
RBB Right bu dl b ch block.
LBB Left b ndle branch block.
Only lim ted by atrial efract ness. No imp lse blocked below th b dle of H s.

retrograde activation of the bundle of His and atria. This indicates that the area(s) of the VSCS which was maximally refractory and thereby prevented antegrade conduction to the ventricles (panel B H_1H_2 interval = 515 msec) was less refractory at the time the retrograde ventricular impulse activated this region and consequently could permit retrograde conduction to the bundle of His (panel C H_1H = 575 msec) This can be explained by the fact that when the ventricles are pre excited ventricular activation initially begins by muscle to-muscle depolarization A few milliseconds later (undetermined) the impulse enters the VSCS This slight delay causes the retrograde impulse to reach the AMR at a time later in the cardiac cycle when it is less refractory This explanation is supported by the fact that the interval from the onset of ventricular depolarization (V) to the retrograde His deflection (H) measures 155 msec which exceeds by 85 msec the longest H V interval which was obtained (panel A H_2V_2 = 70 msec) just prior to failure of antegrade conduction to the ventricle (panel B)

Fig 3 taken from the same patient demonstrates a phenomenon which might be interpreted as an AMR or gate during retrograde conduction In panel A a premature ventricular response (V_s) is elicited at an H_1V interval of 420 msec resulting in delayed retrograde activation of the bundle of His and atria There is a fully compensatory pause following the induced ventricular beat In panel B an earlier stimulus at an H_1V_s interval of 415 msec fails to conduct retrogradely to the bundle of His resulting in an interpolated ventricular beat The next sinus beat is slightly premature due to the ventriculophasic effect of the interpolated beat. The A H interval of the sinus beat shows no effects of retrograde concealed conduction

The results of the findings presented

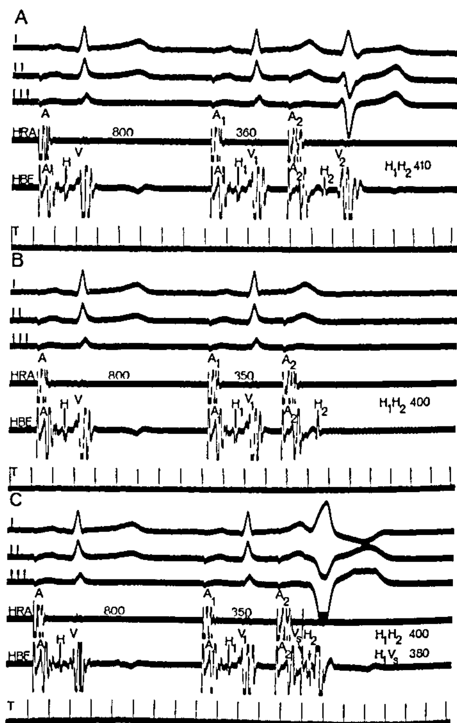


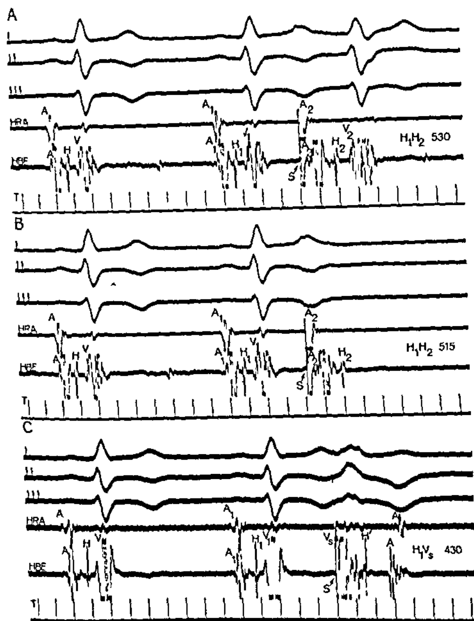
Fig 1 Localization of the site of block of a premature impulse (Patient 6)

In panels A to C records of standard ECG Lead I to III high right atrial electrogram (*HRA*) His bundle electrogram (*HBE*) and time lines (*T*) at intervals of 10 and 100 msec are shown A atrial electrogram *H* His bundle electrogram *V* ventricular electrogram *S* stimulus artifact In panels A to *C* the atria are being paced at a constant cycle length of 800 msec with an A H interval of 85 msec and an H V interval of 45 msec

Panel A A premature atrial depolarization (A_2) is introduced 360 msec after the preceding atrial impulse (A_1) and is conducted with an A_2-H_2 interval of 135 msec and an H_2 V_2 interval of 70 msec associated with a pattern of right bundle branch block (RBBB) and left anterior fascicular block (LAF) The H_1 H_2 is 410 msec.

Panel *B* A_2 is slightly more premature occurring at an A_1 A_2 interval of 350 msec and is conducted with an A_2 H_2 interval of 135 msec H_2 fails to conduct antegradely at an H_1 H_2 interval of 400 msec

Panel *C* The sequence is identical to that of Panel *B* In addition the ventricle (V_s) is simultaneously being stimulated at an H_1 V_s interval of 380 msec Note the antegrade His is still seen at an H_1 H_2 interval of 400 msec



F   Localization of the site of block of a premature impulse (Patient 3) Sinus rhythm is initially present with LAF (−30) in each panel at a cycle length of 900 msec, with an A H interval of 110 msec and an H V interval of 55 msec

Panel A A premature atrial impulse (A) introduced 480 msec after the preceding sinus impulse (A_1) is conducted with an A_2-H interval of 150 msec The resulting prematurely evoked His depolarization (H_2) occurs at an H H interval of 530 msec and is conducted with an H-V interval of 70 msec associated with a pattern of RBBB

Panel B A_2 slightly more premature (A A = 4 0 msec) and conducted with a delay of 150 msec to the bundle of His (H) The H H_2 interval is 515 msec with block occurring distal to the bundle of His

Panel C The ventricle prematurely stimulated at an H V interval of 430 msec, resulting in retrograde depolarization of the bundle of His (H) as well as the atria The V H interval is 155 msec, and the H_1 H interval is 575 msec

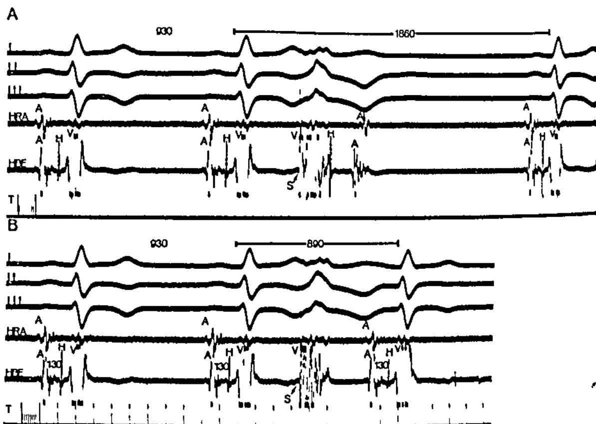


Fig. 3. Retrograde conduction delay and block below the bundle of His (Patient 3). In panels *A* and *B*, sinus rhythm is present at a cycle length of 930 msec. See text for discussion.

Fig. 4. Delay of a premature impulse in the proximal VSCS allowing distal recovery (Patient 1). To the right of each panel is a simultaneous recording of ECG Leads I, II, V_1 and V_6. Pacing stimuli are being delivered through a catheter lying in the coronary sinus and are associated with inverted P waves in Leads II and III. The sequence of atrial depolarization is reversed with the low atrial septum recorded in the HBE preceding the HRA.

In Panels *A* to *D*, the atria are being paced at a constant cycle length of 1,150 msec., and atrial premature depolarizations (APD's) are introduced progressively earlier in the basic atrial cycle. Left anterior fascicular block is present with an axis of > − 60 with a QRS duration of 0.12 sec. The A-H interval is 100 msec. and the H-V interval is 45 msec.

Panel *A*. APD introduced 490 msec. after the last paced atrial beat is conducted with an A_2-H_2 interval of 130 msec. The resulting H_1-H_2 interval is 520 msec.; the premature His depolarization thus evoked is conducted to the ventricle with an H_2-V_2 interval of 70 msec., associated with a pattern of RBBB and LAF.

Panel *B*. APD introduced at an A_1-A_2 interval of 470 msec. conducts to the bundle of His with an A_2-H_2 interval of 140 msec. Block of H_2 occurs at an H_1-H_2 interval of 510 msec.

Panel *C*. APD introduced at an A_1-A_2 interval of 440 msec. conducts with an A_2-H_2 interval of 140 msec. H_2 now occurs at an H_1-H_2 interval of 480 msec. and, although more premature than its counterpart in Panel *B*, is conducted to the ventricle with an H_2-V_2 interval of 210 msec., associated with a pattern of left bundle branch block (LBBB). Note that primary T wave changes are present with the LBBB beat, reflecting the repolarization abnormality obvious in the control beats.

Panel *D*. APD introduced at an A_1-A_2 interval of 430 msec. is conducted to the bundle of His with an A_2-H_2 interval of 145 msec., resulting again in block below the His at an H_1-H_2 interval of 460 msec.

Two HBE were recorded in this instance, utilizing different combinations of bipolar leads from the tripolar catheter. The failure of the blocked H_2 to appear in the lower HBE (Panel *D*) emphasizes how catheter position may lead to the erroneous diagnosis of block within the A-V node.

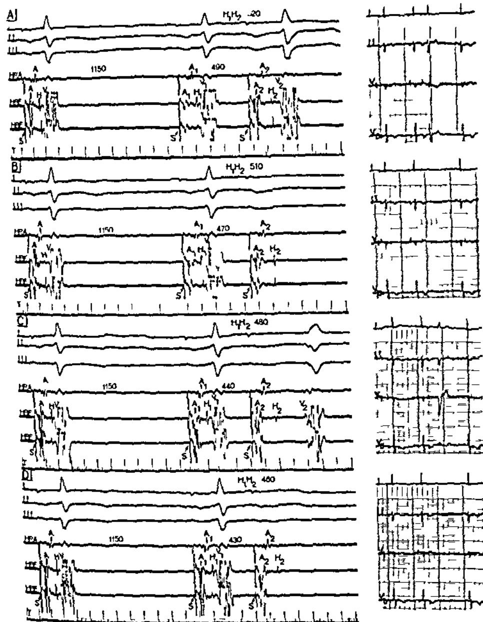


Fig 4 For legend see opposite page.

in Figs 2 and 3 suggest that muscle delay by affording the VSCS recovery time may allow a ventricular response elicited during the ERP of VSCS to propagate retrogradely Additional delay in some area of the VSCS must also be postulated for two reasons (1) No change in configuration or duration of the ventricular beat was observed during progressively more premature stimulation of the ventricle Such changes might have suggested more muscle to muscle propagation as increasing conduction delay was encountered (2) No latency or multiple firing was seen despite significant delays

Fig 4 is an example of differential refractoriness in the VSCS in man (Patient 1) In panel A H_2 arrives in the refractory period of the right bundle branch at an $H_1 H_2$ interval of 520 msec In panel B an

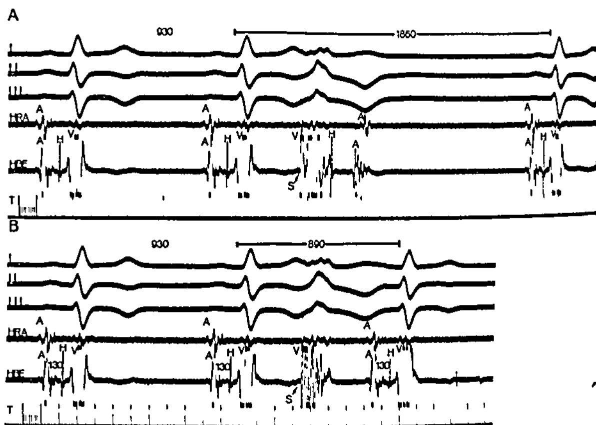


Fig 3 Retrograde conduction delay and block below the bundle of His (Patient 3) In panels A and B sinus rhythm is present at a cycle length of 930 msec See text for discussion

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Fig 4 Delay of a premature impulse in the proximal VSCS allowing distal recovery (Patient 1) To the right of each panel is a simultaneous recording of ECG Leads I II V_1 and V_6 Pacing stimuli are being delivered through a catheter lying in the coronary sinus and are associated with inverted P waves in Leads II and III The sequence of atrial depolarization is reversed with the low atrial septum recorded in the HBE preceding the HRA

In Panels A to D the atria are being paced at a constant cycle length of 1 150 msec and atrial premature depolarizations (APD s) are introduced progressively earlier in the basic atrial cycle Left anterior fascicular block is present with an axis of > − 60 with a QRS duration of 0 12 sec The A H interval is 100 msec and the H V interval is 45 msec

Panel A APD introduced 490 msec after the last paced atrial beat is conducted with an A_2-H_2 interval of 130 msec The resulting H_1 H_2 interval is 520 msec the premature His depolarization thus evoked is conducted to the ventricle with an H_2 V_2 interval of 70 msec associated with a pattern of RBBB and LAF

Panel B APD introduced at an A_1 A_2 interval of 470 msec conducts to the bundle of His with an A_2-H_2 interval of 140 msec Block of H_2 occurs at an H_1 H_2 interval of 510 msec

Panel C APD introduced at an A_1 A_2 interval of 440 msec conducts with an A_2 H_2 interval of 140 msec H_2 now occurs at an H_1 H interval of 480 msec and although more premature than its counterpart in Panel B is conducted to the ventricle with an H_2 V_2 interval of 210 msec associated with a pattern of left bundle branch block (LBBB) Note that primary T wave changes are present with the LBBB beat reflecting the repolarization abnormality obvious in the control beats

Panel D APD introduced at an A_1 A_2 interval of 430 msec is conducted to the bundle of His with an A_2-H_2 interval of 145 msec resulting again in block below the His at an H_1 H_2 interval of 460 msec.

Two HBE were recorded in this instance utilizing different combinations of bipolar leads from the tripolar catheter The failure of the blocked H_2 to appear in the lower HBE (Panel D) emphasizes how catheter position may lead to the erroneous diagnosis of block within the A V node

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to ERP's (570 and 470 msec) of the VSCS in this patient. The limitation of the usual manner of defining the ERP is readily apparent in a patient such as this.

Fig. 5 demonstrates an interesting phenomenon observed in one patient (Patient 3). Appropriately timed spontaneous premature junctional extrasystoles were confined within the conduction system proximal to the AMR. In panel A a prematurely evoked His depolarization occurs at an H_1H_2 interval of 520 msec, which is less than the ERP of the VSCS for this patient (see Table I) and thus fails to conduct to the ventricle. In panel B, following the same preceding cycle length, a spontaneous His extrasystole occurs at an H_1H_2 interval of 500 msec and also fails to propagate to the ventricle. However, it does propagate retrogradely and thus simulates electrocardiographically a blocked premature atrial beat as evidenced by the inverted P waves in Leads II and III. Junctional beats occurring outside the ERP of the VSCS (i.e., at an H_1H_2 interval greater than 530 msec) conducted successfully to the ventricle. In three patients (1, 2, and 4) the ERP of the VSCS was shortened by decreasing the basic cycle length of atrial pacing. In two patients (1 and 4) the ERP of the VSCS was sufficiently shortened so that block below the His during premature atrial stimulation could not be elicited. Atrial refractoriness was observed to decrease in all patients at higher paced rates.

Discussion

Block of premature impulses distal to the bundle of His has been described in animal studies[2,3,11,14] and in man.[15,16] In addition, block of retrograde propagation of ventricular depolarization has been shown to occur at various levels of the VSCS.[4,17,18]

In the present study, an AMR was demonstrated in the human heart which limited the propagation of premature impulses arising on either side of it. When block of premature supraventricular impulses occurred distal to the bundle of His in our selected patients, the ventricular muscle was invariably excitable at an earlier point in diastole than that at which antegrade conduction failed. This confirms in man that muscle refractoriness is not the cause of such block. Block of retrograde conduction below the AMR (Fig. 3) provides a mechanism in man for the failure of some interpolated premature ventricular beats to show the effects of concealed conduction in the A-V node. This may also provide protective mechanism against premature ventricular beats initiating arrhythmias on the basis of macroreentry utilizing the proximal portions of the VSCS.

In vitro studies have indicated that during antegrade conduction, premature impulses with a coupling interval shorter than the refractory period of the AMR can be successfully conducted when sufficient delay in a more proximal region of the VSCS allows the more distal AMR to recover.[6] Our findings of a similar phenomenon (Fig. 4) in man are in agreement.[19] Thus, a "gap" in conduction may occur because of delay in the VSCS analogous to the A-V nodal delay responsible for the A-V nodal gap phenomenon. There is an essential difference, however, between these two mechanisms. The H_1H_2 interval at which conduction resumes in the "A-V nodal gap" is longer than that at which block below H_2 occurs, while in the "VSCS gap" the H_1H_2 interval is shorter than that at which block below H_2 occurs. In the former, A-V nodal delay allows the AMR to recover; in the latter, delay in some area of the VSCS proximal to the AMR allows it to recover. Since conduction resumes at closer coupling intervals, the phenomenon of delay in the VSCS allowing recovery represents another type of so-called "supernormal" conduction.

The approach of the present study may be useful in future studies on the effects of pharmacological agents which depress conduction in the VSCS, because it emphasizes the need for independent assessment of the refractoriness of muscle and specialized conducting tissues.

Summary

The area of maximum refractoriness (AMR) or "gate" in the ventricular specialized conduction system (VSCS) has not been previously demonstrated in the human A-V conduction system. Animal studies have shown an AMR proximal to the Purkinje-muscle junction.

Seven patients were studied using His

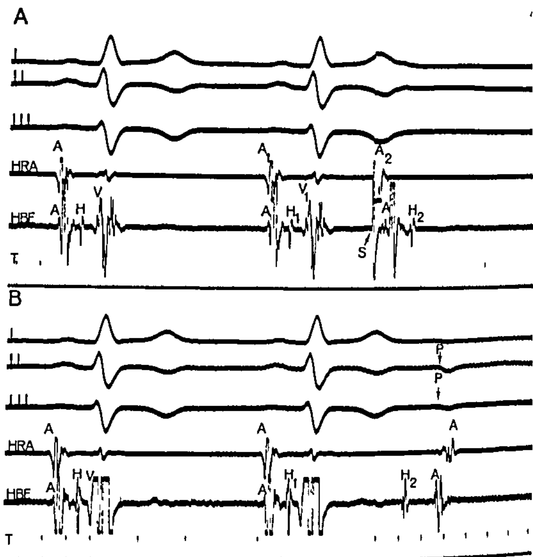


Fig. 5. Concealed junctional extrasystole simulating a blocked premature atrial impulse (Patient 3).
Panel A. Sinus rhythm is present with a cycle length of 880 msec. The A-H interval is 100 msec, and the H-V interval is 55 msec. Note the normal sequence of atrial depolarization proceeds from the HRA to the low atrial septal deflection recorded in the HBE. An APD introduced at an A_1A_2 interval of 480 msec is blocked below the bundle of His with an H_1H_2 interval of 520 msec.
Panel B. Following the same preceding cycle length a spontaneous His extrasystole (H_2) occurs at a slightly shorter H_1H_2 interval of 500 msec and fails to conduct antegradely. It is, however, retrogradely conducted to the atria with an H-A interval of 150 msec and is associated with an inverted P wave in Leads II and III. The polarity of the His deflection as well as the sequence of atrial depolarization is reversed.

earlier His bundle response at an H_1H_2 interval of 510 msec fails to propagate to the ventricle. In panel *C* H_2 arrives at an H_1H_2 interval of 480 msec and is conducted with a very long H-V interval of 210 msec. Ventricular depolarization yields a pattern of left bundle branch block (LBBB), suggesting that delay occurred proximal to the AMR in the right-sided VSCS, allowing recovery of the latter with resultant propagation to the ventricle. In panel *D* H_2 is even more premature, at an H_1H_2 interval of 460 msec, and once again fails to conduct to the ventricle. Refractory periods were carefully repeated in this patient decreasing the prematurity of the test stimulus by 2 msec intervals. On each determination (*a*) all H_1H_2 intervals $\geq$ 520 msec conducted to the ventricle; (*b*) H_1H_2 intervals between [illegible] and 510 msec resulted in block below H; (*c*) conduction resumed between intervals of 505 and 470 msec with LBBB and a long H_2V_2 interval; and (*d*) H_1H_2 intervals less than 470 msec again resulted in block below H_2. For this reason Table I indicates

A new roentgenographic assessment of anatomic deformity in calcific aortic stenosis

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The aortic valve can be visualized as if looking directly into the orifice by btaining roentgenograms with the x ray eam directed through the heart on a line rom the right axilla to the left iliac crest [1] Even though there is variation of the patial orientation of the aortic valve tests in patients with aortic ball valve prostheses (in whom the area of the orifice is precisely known) showed that the orifice can be measured by this method with 90 per cent accuracy in 80 per cent of patients [1] Aortograms taken at this projection have been utilized effectively to measure the functional cross sectional area of the aortic valvular orifice in normal subjects as well as patients with diseased aortic valves [1,2] The injection of contrast material is neces sary to evaluate the orifice if the valve is not calcified In the presence of valvular calcification plain roentgenograms by the use of this projection can show the calcified outline of the orifice By noninvasive roentgenographic techniques therefore the pathologic deformity of the stenotic cal cific aortic valve can be defined with close approximation to the actual specimen In this communication the technique is il lustrated and patients are described in whom the method appeared to be of prac tical value

Methods

Plain films of the chest are obtained with the patient supine and the x ray beam di rected through the heart at a 45 degree superior elevation in the frontal plane and a 0 degree elevation in the sagittal plane [1] At this angle the aortic valve can be visual ized as if looking directly into the orifice Any dimension of the orifice that is outlined by calcium can be measured from the roentgenogram In order to compensate for magnification the position under the chest of the calcified valve is located by fluoros copy Localization of the valve in this way permits one to measure the distance from the x ray tube to the valve (target to-object distance) Dimensions measured on the roentgenogram are assessed after proper compensation for magnification by the fol lowing equation

$$\text{Actual length} = \text{Apparent length}\ \frac{\text{Target to-object distance}}{\text{Target to film distance}}$$

An approximate exposure time of 1/12 sec at 400 Ma and 100 kv has been ade

From the Department of M d l Uni i y of Oklah m School of M dicine and V te a s Administ tio Ho p tal Oklal m C ty Okla.
S pported l part by th V t rans Admi i tr tl R sea ch Service and Okl hom Heart Associati n.
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bundle electrograms Single atrial premature depolarizations (APD) were introduced progressively earlier during the basic atrial cycle, until a point was reached where the APD no longer conducted to the ventricles The region of block in these seven selected patients was distal to the bundle of His Single ventricular depolarizations were then likewise introduced prematurely throughout mid late diastole In all seven patients the ventricle could be depolarized earlier in the basic cycle (30 to 220 msec) than the point at which block below the His occurred, localizing the AMR between the bundle of His and the ventricular muscle A similar AMR was found during retrograde conduction

A mechanism analogous to the A V nodal "gap phenomenon exists in the VSCS Thus, late premature atrial impulses may fail to conduct distal to the bundle of His while earlier beats encounter delay in an area of the VSCS proximal to the AMR allowing propagation to the ventricle This represents another mechanism of so called supernormal conduction

The present study emphasizes simultaneous evaluation of the refractory state of specialized cardiac conducting tissue and muscle Such an approach may be useful in future studies of drugs which depress subjunctional tissues

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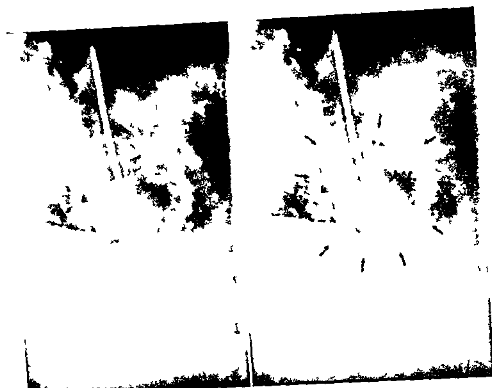
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F ? Roentgenogram of the same patient taken at a projection specifically designed to show the aortic valve as if looking directly into the orifice The calcified annulus appears circular indicating negligible distortion of the projected image The orifice shown within the calcified valve appears as an eccentric elongated radiolucent zone A 2 mm. diameter pacemaker catheter is positioned in the right ventricle and is superimposed over the valvular orifice Dimensions of the orifice can be judged by comparison with the diameter of the catheter For clarity the orifice is outlined by dots in the duplicate illustration at right The annulus is shown by arrows



Fig. 3 Excised aortic valve (same patient as in Figs. 1 and 2) Lines on the grid in the background are spaced at 1 mm. intervals.



Fig 4 Roentgenogram of excised aortic valve (same valve as in Fig 3) Radiopaque dots are placed at 1 cm intervals. The central radiolucent zone is the orifice. A nearly radiolucent (gray) rim of tissue is shown between the lumen and calcified region.



Fig. 1. Posterior anterior chest film of a patient showing heavy deposits of calcium in the region of the aortic valve (arrows).

quate in most patients. A grid cassette with high speed Radelin* screens and GAF x film† is routinely utilized.

The aortic valve illustrated in this study was re-evaluated after it was surgically excised at the time of insertion of a ball valve prosthesis. The leaflets were reconstructed immediately after they were removed in the operating room. Photographs and roentgenograms of the excised valve were obtained. The configuration and dimensions of the valve were evaluated from these films.

Results

Heavy deposits of calcium in the region of the aortic valve of a man with clinical evidence of severe aortic valvular disease were shown on chest films (Fig. 1). At cardiac catheterization a 58 mm. Hg peak pressure gradient was measured across the aortic valve. Moderate aortic regurgitation was shown on cine aortograms.

A plain roentgenogram of the calcified valve was taken with the patient supine and the x-ray tube elevated 45 degrees in the frontal plane. The configuration of the orifice, outlined by calcium, is shown (Fig. 2).

At surgery a heavily calcified valve was removed. The configuration of the orifice was similar to that shown on the 45 degree angle roentgenogram (Fig. 3). Roentgenograms of the excised valve also showed a similar configuration (Fig. 4). The central radiolucent area of this roentgenogram represents the actual lumen as shown on the photograph of the valve. Between the lumen and heavy calcific deposits there is a less radiolucent fibrotic rim (Fig. 4). This rim is completely radiolucent and, therefore, inapparent on the roentgenogram of the valve taken prior to surgery (Fig. 2). The dimensions measured from this oblique chest film correspond to the dimensions outlined by calcific deposits. The length of the orifice appeared to be 2.8 cm. on the preoperative film of the orifice (Fig. 2) and 2.5 cm. on the roentgenogram of the excised valve (Fig. 4). Similarly, a sample width of the valve appeared to be 0.7 cm. on the special chest film and 0.6 cm. on the postexcisional film. Since a noncalcified inner rim of fibrous tissue was present, the actual dimension of the orifice (length, 1.6 cm.; width, 0. cm.) were somewhat smaller (Fig. 3).

Discussion

This method is particularly advantageous because it is noninvasive and the results directly reflect the morphology of the abnormal aortic valve. In patients with heavily calcified valves, the technique permits a preoperative assessment of the anatomy of the deformed valve that closely corresponds to the configuration and dimensions of the actual specimen.

Evaluation of the results requires recognition of the fact that the cross-section area of the actual orifice will be smaller than the area outlined by calcium. In some patients, however, the area enclosed by calcium will be small enough to indicate critical stenosis, irrespective of the presence of a central noncalcified radiolucent rim. This was demonstrated in three patients in whom the area circumscribed by calcium was 0.6, 0.7, and 0.8 sq. cm., respectively, and in whom nearly identical orifice areas were measured at surgery. Consequently, the method in some patients can be utilized to determine if a valvular deformity is severe enough to warrant a surgical intervention. In appropriate patients, th

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Ejection fraction in anomalous origin of the left coronary artery from the pulmonary artery

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The indications for surgery in the case of anomalous left coronary artery from the pulmonary artery are not readily agreed upon Nadas and associates[1] suggested that if there is a left to right shunt at pulmonary arterial level demonstrated by selective arteriography ligation of the anomalous vessel should be carried out Nora and colleagues[2] suggested that the child with anomalous left coronary artery arising from the pulmonary artery be managed medically until the age of 5 years when definitive surgical therapy could be undertaken Perry and Scott[3] divided infants and children with this anomaly into three groups depending on the degree of collateral circulation and assigned to each group a different type of management Prompted by these differences of opinion and the fact that we have had 5 cases surgically treated by ligation of the anomalous left coronary artery we decided to look for other parameters that would help selection of patients with this anomaly for ligation of the vessel We have chosen the ejection fraction because it is a quantitative measurement which has good correlation with myocardial function[4]

Materials and methods

Between 1966 and 1971 5 cases of anomalous left coronary artery from the pulmonary artery were seen at Albany Medical Center Hospital In addition 5 cases were found in the literature on whom ejection fraction or ventricular volumes were reported[4-6,9] Eight of these 10 patients were treated surgically 6 by ligation of the anomalous coronary artery one by suture of orifice through an arteriotomy and one by anastomosis of anomalous vessel to the aorta Two patients were treated medically Of the 8 that had surgery there were 3 girls and 5 boys The ages ranged from 5 weeks to 12 years Three of these patients survived surgery Of the 2 medically treated the one alive was 9 years old when diagnosed the other died at the age of 5½ months All were investigated by angiocardiography but pressure and oxygen saturation data were available to us for only 6 patients Of the 6 that died autopsy information was available to us in 4 cases

In 8 patients the ejection fractions were calculated from preoperative angiocardiograms In the remaining 2 they were calculated from postoperative angiocardio

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method could therefore eliminate the necessity of cardiac catheterization

Summary

By utilization of noninvasive roentgenographic methods one can define the anatomic deformity of calcified aortic valves with close approximation to the actual specimen. This is accomplished by visualization of the area circumscribed by calcium on plain films obtained at a projection specifically suited for this purpose. Films are obtained as if looking directly into the orifice by directing the x-ray beam through the heart on a line from the right axilla to the left iliac crest (45 degree superior elevation in the frontal plane). The dimensions outlined by calcium can be reliably measured. Consequently, the dimensions of the orifice can be closely approximated. In occasional patients with heavily calcified, severely stenotic aortic valves the technique may obviate the necessity of cardiac catheterization.

The author would like to thank Dr James M Hartsuck for his skillful surgical dissection of the aortic valve illustrated in this study

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Pressures						Time
RA	RV	PA	LA	LV	Ao	
				95/0	95/60	Preop
9 3	76/6	26/12	16/10 wedge	1 0/3	120/80	Postop
0	50/5	20/10 M = 15		110/15	110/60 M = 80	Preop
8/2 M = 6	40/4	40/25 M = 32		90/10	90/60	Preop
	40/5	37/10 M = 22		90/20	80/50 M = 62	Preop
2	30/6	30/15 M = 20			50/40	Preop
2	8/10	33/20 M = 26		80/35	80/60 M = 70	Preop
6 V = ? M = 1	46/6 E D	40/14 M = 20	A = 15 V = 8 M = 6		112/86 M = 90 FA	Preop
= 4 A = 3 M = 5	37/4 E D	36/21 M = 24		75/12 19 E D		Postop

mean op. = operat PA = p lm nary rtery RA = g t atri m RV = g t entr cle SVC = super na ca a.

a step up in oxygen saturation who survive regardless of therapy employed Group 2 those patients who have a left to right shunt at the pulmonary arterial level demonstrated angiocardiographically which is not large enough to be detected by oxygen saturation (in this group there is no definite difference between those treated surgically and those treated medically surgery should be undertaken when the patient reaches 3 years of age) Group 3 those patients with no left to right shunt The only therapy is anastomosis of the anomalous left coronary artery to the aorta

Of the 44 cases with hemodynamic and angiocardiographic studies mostly collected from the literature by Perry and Scott,[4] 18 were in Group 1 22 in Group 2 and 4 in Group 3 Since the mean age of Group 1 was 6 1 years it would seem that most patients seen during the first year of life will fall into Groups 2 and 3 All 4 patients with preoperative hemodynamics and angiocardiographic data seen at Albany Medical Center Hospital were in Group 2 The authors believe that the ejection fraction would be of a particular help in the selection of Group 2 and 3 patients for surgery It would seem that those patients with ejection fractions more than 0 55 would be good candidates for surgery The vessel should be anastomosed to the aorta if it is large enough to accomplish the procedure Those with ejection fractions less than 0 35 have a poor prognosis regardless of the method employed and should be treated by vigorous medical therapy Since none of the patients in this study had an ejection fraction between 0 35 and 0 55 the indications for surgery in this group should await further study

The authors believe that in addition to the symptoms clinical findings electrocardiograms and chest x ray the ejection fraction may also be used to follow the progress of these patients and to assess the surgical result Determination of the ejection fraction by ultrasound[11, 12] could be the method of choice in the follow up of these patients

Summary

The ejection fraction of 10 patients with anomalous origin of the left coronary artery from the pulmonary artery has been studied Five were seen at Albany Medical

Table I. Cardiac catheterization data

Patient	Oxygen saturations							
	IVC	SVC	RA	RV	PA	LA	LV	Ao
1 C C	69	79	80	78	81		96	96
2 (Bookstein[6]) D V								
3 D I	74	74	77	76	76		9[illegible]	91
4 C W	67	69	62	64	63		95	9[illegible]
5 (Graham et al [4])								
6 J W	71		67	55	66			
7 M W	49	50	51	49	49		89	91
8 (Bookstein[6]) D M								
9 (Wagner et al [9]) D B		36 0	86 9	85 0	83 4	96 5		FA 96
		64 5	63 0	57 8	62 5		99 5	
10 (Bookstein[6]) J H								

Abbreviations Ao = aorta E D = end diastolic F A = femoral artery IVC = Inferior vena cava LA = left atrium LV = left ventricle

grams In our patients (Nos 1 3 4 6 and 7), ejection fractions were calculated according to the method described by Kennedy and associates[5] from single plane cine angiocardiograms in the anteroposterior projection Of the 5 cases collected from the literature the ejection fraction for Patients 2, 8, and 10 were calculated from ventricular volumes reported by Bookstein [6] The method for determining the ejection fraction in Patient 5 was that of Dodge and Sandler [8] In Patient 9 ejection fractions were determined from ventricular volumes measured by the method of Dodge and Sandler [8] The patient, D B, was reported in 1967[9] to be one year and 9 months old and doing well Later, she developed congestive heart failure and died at the age of 2 years 9 months [10] The Kennedy group[5] has shown that ventricular volumes and ejection fractions calculated from biplane cineangiocardiography and from single plane angiocardiography correlate well with each other [5]

Results

Table I presents the cardiac catheterization results and Table II presents the ejection fractions of the 10 patients studied in this report

The 4 patients who survived have ejection fractions between 0 84 and 0 55 The 6 patients who died had ejection fractions between 0 36 and 0 13

Discussion

Graham and co workers[4] state that the ejection fraction has good correlation with myocardial function and that if the ejection fraction drops below 0 50 it is indicative of myocardial dysfunction Our studies support this conclusion for those patients with an ejection fraction above 0 55 did well and those below 0 36 died Our results indicate the possibility of determining a scale of ejection fractions,[2] and that somewhere between 0 35 and 0 55 is the point above which surgery can be undertaken with reasonable safety and below which the prognosis is poor with or without surgery

Perry and Scott[3] classified the infant and children with anomalous left coronary artery arising from the pulmonary artery into three groups Group 1 those patients with a left to right shunt at the pulmonary arterial level demonstrated by

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Table II. Ejection fractions in anomalous left coronary artery from the pulmonary artery

Patient	*Cath pre or postop*	*Ejection fractions*	*Evidence of shunt*	*Surgery*	*Prognosis*
1 C C	Preop		Angio – RCA to collateral to ALCA to PA		
	Postop	0 84		Yes ligation at 6 mo	Alive at 9 yr
2 (Bookstein[8]) D V	Preop	Approx 0 72	Angio – RCA to collateral to ALCA to PA	No	Alive at 9 yr
3 D T	Preop	0 67	Angio – RCA to collateral to ALCA to PA	Yes at 12 yr suture of orifice	Alive at 15 yr
4 C W	Preop	0 55	Angio – RCA to collateral to ALCA to PA	Yes ligation at 6 mo	Alive at ?? mo.
5 (Graham et al[4])	Preop	0 36	Angio – RCA to collateral to ALCA to PA	Yes ligation at 6 wk	Died second postop. day at 6 wk
6 J W	Preop	0 31	Angio – RCA to collateral to ALCA to PA	Yes ligation at approx 9 mo	Died 6 mo postop. in severe CHF at 15 mo. of age
7 M W	Preop	0 23	Angio – RCA to collateral to ALCA to PA	Yes ligation at 2½ mo	Died postop at 2½ mo of age
8 (Bookstein[8]) D M	Preop	0 21	None demonstrated	No surgery just medical management	Died at home at 3 mo of age
9 (Wagner et al[9]) D B	Postop	0 184	Small shunt at surgery	Yes ligation at 5 wk	Died at 2 yr 9 mo in severe CHF
10 (Bookstein[8]) J H	Preop	0 13	Angio – RCA to collateral to ALCA to PA	Yes anastomosis to aorta at 4 mo of age	Died a few hours postop at 4 mo. of age

Abbreviations ALCA = anomalous left coronary artery Angio = angiography Approx = approximately Cath. = catheterization CHF = congestive heart failure RCA = right coronary artery

Center Hospital and 5 were collected from the literature The 6 patients who died had an ejection fraction less than 0 36 The 4 survivors had an ejection fraction more than 0 55 It has been suggested that this measurement will help in the selection of patients for surgery and the follow up of patients with this anomaly

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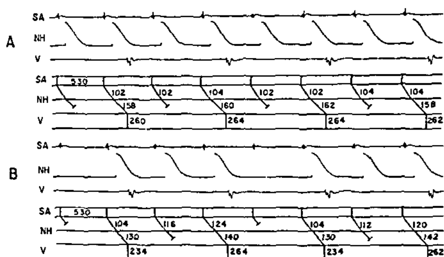


Fig 1 *A* and *B* Transmembrane potential from an NH fiber (*NH*) are shown with surface electrograms recorded from the S-A nodal region (*SA*) and the ventricles (*V*) Sinus rhythm with little variation of the cycle length (approximately 530 msec) is present The ladder diagrams show sequence of A V conduction with A NH NH V and total A V conduction time in milliseconds Regular 2 1 block with fixed long A V interval (*A*) and with alternation of A V interval (*B*) are seen For details see text

perfusion fluid was saturated with 95 per cent O_2 + 5 per cent CO_2

A ventricular electrogram was recorded by two small surface electrodes attached to the right ventricular apex and to the left ventricular base In some experiments a small bipolar electrode with an interelectrode distance of 1 mm was attached adjacent to the S A node to record an atrial electrogram Most preparations were driven at a constant rate by square wave pulses of twice threshold intensity through a bipolar stimulating electrode placed near the S A node The rate of stimulation in individual hearts was set 10 to 15 beats per minute higher than the intrinsic sinus rate in the majority of experiments while rapid atrial stimulation at the rate of 300 per minute or higher was used in others to simulate atrial flutter A V conduction was studied in some hearts under spontaneous sinus rhythm Glass microelectrodes were used to record transmembrane potentials from various regions of the A V junction The potential were amplified by a neutralized input capacity amplifier and Tektronix amplifiers A Grass camera was used to photograph tracings on a Tektronix oscilloscope Records were obtained from experiments in which A V block developed

Examples of clinical electrocardiograms (E CG s) showing similar conduction abnormalities were selected from the files of the Heart Station of the Hahnemann Medical College and Hospital unless otherwise specified

Results and comments

I A V block during slow sinus or atrial rhythm Since the levels of concealment or propagation failure in the more common varieties of second degree A V block were previously reported [15] relatively uncommon types of A V conduction abnormalities including advanced second degree block and multiple levels of block will be presented Fig 1 *A* shows a regular 2 1 A V conduction in the presence of a sinus rhythm averaging 113 beats per minute Transmembrane recordings from the distal NH (node–His) region reveal a propagated action potential with an apparently normal rate of depolarization following each atrial activation or with 1 1 conduction across the A V node Every other NH potential is however not followed by ventricular excitation indicating a 2 1 block within the His Purkinje system Bizarre and wide complexes of the ventricular electrogram and a markedly prolonged His Purkinje conduction time (160 msec) clearly show the presence of intraventricular conduction delay Conduction time from the S A node to the distal NH fiber measures 102 to 104

Experimental and laboratory reports

Levels of concealment in second degree and advanced second degree A-V Block

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The effects of blocked cardiac impulses on subsequent conduction were first described by Engelmann in 1894,[1] and several experimental observations elucidated some of the underlying mechanisms early in this century [2-4] Similarly the effects of premature systole on impulse formation in the A V junctional region were interpreted by Scherf and Shookhoff[5] as an indication of partial retrograde penetration of the ectopic impulse However it was after the reports of Langendorf and associates[6,7] that the concept of concealed conduction became an indispensable tool in analyzing complex clinical arrhythmias Later electrophysiological studies utilizing either microelectrode technique[8-16] or close bipolar electrodes[8] have established the validity of this concept It should be stressed that a majority of those studies dealt with concealed conduction of premature impulses[8-12] or impulses from the fibrillating atria [13,14] and few such reports are available on concealment of impulses in the presence of a regular atrial or ventricular rhythm [8,14,16] More recently the advent of His bundle electrography has made it possible to study the phenomenon of concealed conduction in man, and several papers[17-19] have mostly reconfirmed the results of earlier microelectrode studies demonstrating the levels of propagation failure in various types of A V block [15]

In this paper different levels and sequences of 'concealment' in second degree and advanced second degree (where two or more impulses are consecutively blocked) A V block are demonstrated utilizing microelectrode techniques in order to further illustrate the complexity of abnormal A V conduction Possible electrophysiological mechanisms underlying these varieties of A V conduction disturbance are discussed and correlation of these experimental findings with clinical observations is attempted wherever possible

Material and methods

Experimental studies were carried out in isolated perfused rabbit hearts using techniques of isolation and perfusion reported previously [20] We used a modified Chenoweth's solution of the following composition in millimoles per liter NaCl 119 8 KCl 4 5 CaCl 2 4 MgCl 2 1 $NaHCO_3$ 25 0 and dextrose 10 0 The

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blocked atrial impulses penetrate deeper into the A V junction the subsequent P R interval is long while impulses blocked high are followed by a shorter P R interval They implied that concealed conduction in this case was the result of two levels of block.[21]

Considering the experimental records shown in Fig 1, the second interpretation appears more plausible as originally suggested by Katz and Pick.[21] It should also be emphasized that the QRS duration measured 0 14 second showing intraventricular conduction delay a finding further in keeping with our experimental observations

Another example of 2 1 A V conduction with alternation of short and long A V intervals is illustrated in Fig 3 *A* In this instance four cycles of 2 1 A V response are shown at the beginning of the record with the A V interval of conducted beats measuring 202 138 190 and 150 msec sequentially This alternation may appear similar to that seen in Fig 1 *B* However a striking difference in this instance is that failure of transmission of every other atrial impulse always occurs proximal to the NH fiber from which transmembrane potentials are recorded indicating intranodal block is the sole conduction disturbance It must also be pointed out that the His Purkinje conduction time remains constant and almost normal There is no widening of the ventricular complex in the electrogram Thus in sharp contrast to the records in Fig 1 intraventricular conduction is not disturbed

Although this may appear as only one level of block alternation of the A V interval still resulted from different levels of penetration into the node as suggested by the amplitude of the non propagated responses In comparison with the local responses of the NH fiber following the second and sixth atrial impulses that following the fourth impulse appears slightly greater (Fig 3 *A* asterisk) suggesting a somewhat deeper penetration into the A V node. This causes a prolongation of the intranodal conduction time in the succeeding conducted beat (fifth atrial impulse)

Following these cycles of 2 1 response a period of 4 1 A V conduction is seen During 4 1 conduction the second non conducted impulse usually produces a slightly greater local response than the first and third blocked impulses Similar sequence has been postulated in clinical ECG s which might be termed as abortive 2 1 conduction [7,21] It is also interesting to note that this abortive 2 1 transmission occurs when a longer A V interval is expected from the previous sequence of alternation The long pause due to block of three successive atrial impulses is terminated by a conducted beat with a shorter A V interval Although the transition from 2 1 to 4 1 A V conduction ratio in this instance followed an alternation of the A V interval such a transition sometimes was preceded by several cycles of 2 1 block with progressive prolongation of the A V interval in conducted beats (not shown)

In Fig 3 *B* a record obtained three minutes after Fig 3 *A* three cycles of 2 1 block are followed by periods of 3 1 and 4 1 A V conduction During 2 1 conduction transmembrane record from an N (true nodal) fiber shows alternating deeper penetration of the blocked atrial impulses again associated with an alternation of the A V interval (160 138 and 160 msec) Following a greater local response (deeper penetration of the blocked impulse) depolarization of the N fiber is slower showing a notch on phase O (arrows) Such notching of phase O or marked step formation preceding a more rapid depolarization may suggest decremental conduction or inhomogeneous conduction [22] From the preceding sequence of alternation the sixth atrial impulse is expected to show a less deep penetration Instead this impulse again penetrates deeper as manifested by the magnitude of the local response Block of the seventh atrial impulse causing a 3 1 conduction ratio is most likely a result of this unexpected deeper penetration of the sixth impulse Thus in this particular instance of 3 1 conduction due to intranodal block the first blocked impulse penetrated deeper into the N region than the second Such sequence has been termed an abortive attempt at 3 2 conduction [7,21]

In contrast to the pattern of 3 1 conduction in Fig 3 *B* records obtained earlier in the same experiment showed a different sequence of 3 1 conduction (Fig 4 *A*) In this instance 3 2 A V conduction showing

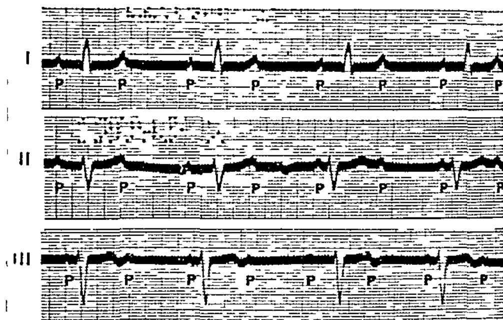


Fig 2 Clinical electrocardiogram showing 2 1 A V conduction with widened QRS A V interval is either continuously long short or alternating See text for discussion (From Katz L N and Pick A Clinical electrocardiography Part I Arrhythmias Philadelphia 1956 Lea & Febiger Fig 339 Reproduced with permission)

msec Intra atrial conduction time was 35 msec at this time (from other records) Hence intranodal conduction time was prolonged to 67 to 69 msec

In Fig 1 *B*, taken 3 minutes after the record *A*, 2 1 A V conduction is still present as seen in the ventricular electrogram However there is now alternation of short (234 msec) and long (262 to 264 msec) A V intervals This resulted in an alternation of the ventricular cycles The mechanism for this alternation is apparent in the action potential recording from the NH region, where every fourth atrial beat fails to evoke a propagated response Thus, there is 4 3 conduction across the A V node with block of the fourth impulse above the NH fiber Progressive prolongation of the intranodal conduction time of the Wenckebach type is evident prior to the failure of nodal transmission However the second of these three impulses successfully travers ing the A V node is blocked below the distal NH region as in Fig 1 *A*, permitting only the first and the third atrial impulses to be conducted to the ventricles The His Purkinje conduction time in transmission of the third atrial impulse (140 msec) is clearly longer than in the first impulse (130 msec), most probably a result of partial penetration of the second impulse into the His Purkinje system Following the block of an impulse above the NH region, both the intranodal and His Purkinje conduction times are shortened, resulting in a shorter A V interval Hence, alternation of short and long A V conduction times in the presence of regular 2 1 block in this instance was caused by two levels of conduction disturbance with alternation of subnodal and intranodal block It should be noted that the longer A V intervals in Fig 1 *B* are almost identical to the A V interval in Fig 1 *A*, where failure of propagation always occurred below the distal NH region However, intranodal and subnodal conduction times are different in these two instances

A clinical ECG with conduction phenomena similar to these experimental records is shown in Fig 2 In this instance of regular 2 1 A V block the P R intervals of the conducted beats fall into two categories one prolonged to 0 34 second and the other normal at 0 16 second All conducted beats in Lead I show the longer P R interval while the last three conducted beats in Lead III show alternation of short and long P R Katz and Pick [1] offered two alternative explanations (1) There are two A V conduction pathways both of which are depressed Both permit transmission of alternate impulses one at a normal speed and the other at a slow speed (2) When

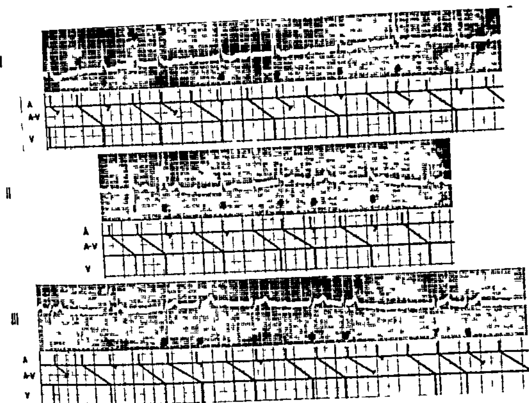


Fig 5 Electrocardiogram showing 2 1 A V conduction with P R alternation and 3 2 and 4 2 conduction ratios in the presence of normal QRS duration (From Langendorf R Am Heart J 35 542 1948 Fig 7 Reproduced with permission)

turbance could actually be found in the transmembrane potential record Following repolarization of this NH fiber after the successful propagation of the first atrial impulse the resting membrane potential is gradually decreased by what appears to be a diastolic depolarization or a step formation prior to phase O of the next action potential This results in a decreased rate of phase O depolarization which may slow conduction in the immediately distal A V transmission system possibly the His bundle Hence Wenckebach periodicity in this instance can be attributed predominantly to a depressed intranodal conduction

On the other hand Fig 4 *B* shows a 4 2 conduction ratio a still rarer type of advanced second degree A V block This is an earlier part of a long continuous record partly shown in Fig 4 *A* Following transmission of two atrial impulses to the ventricles with a progressive prolongation of the A V interval two consecutive atrial impulses are blocked within the A V node The sequence of concealment is similar to that during a 3 1 conduction in Fig 4 *A* with the second non-conducted impulse penetrating somewhat deeper than the first Such 4 2 conduction may sometimes follow a shortening of the A V interval in the second conducted beat (unpublished observation)

Nevertheless Figs 3 and 4 illustrate that intranodal conduction disturbance alone can produce any A V conduction ratio with slightly different levels of concealment including (1) 2 1 conduction with alternating short and long A V intervals (2) transition between 2 1 and 4 1 conduction (3) 3 1 conduction mixed with 2 1 conduction (4) 3 1 conduction mixed with 3 2 conduction and (5) a 4 2 conduction ratio That all these varieties should be and could be explained by a more comprehensive electrophysiological concept will be discussed later Possible clinical examples of these conduction abnormalities are presented in Fig 5

Lead I of Fig 5 shows an alternation of

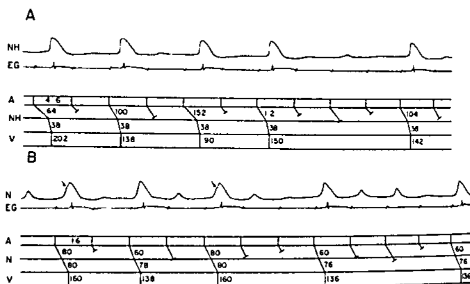


Fig. 3. *A* and *B*. Transmembrane potentials from either NH region (*NH*) or N region (*N*) and an electrogram (*EG*) are shown. The electrogram shows both atrial and ventricular deflections. S-A nodal area is stimulated at a cycle length of 416 msec. Explanation for the ladder diagram is similar to Fig. *1*. A-V conduction ratios between 2:1 and 4:1 are present. See text for discussion.

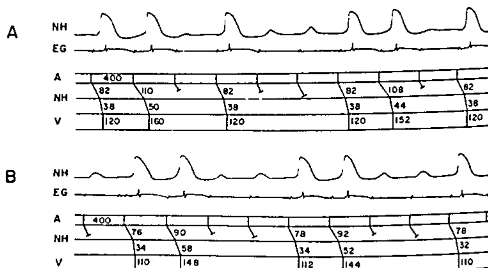


Fig. 4. *A* and *B*. Records from the same experiment as in Fig. *3*. 3:2 and 3:1 conduction (*A*) and a 4:2 conduction ratio (*B*) are present. Abbreviations are the same as in Fig. *3*. See text for discussion.

Wenckebach phenomenon alternates with a 3:1 response. During this period of 3:1 conduction, the first non-conducted impulse is blocked higher within the A-V node than the second non-conducted impulse as judged from the amplitude of local responses in a distal NH fiber. A similar sequence of progressively deeper penetration into the A-V node was previously reported during a transition from 2:1 to 3:1 conduction.[15]

Another point of interest in Fig. 4 *A* is the structure of the Wenckebach phenomenon. As observed in most (but not all) examples of second degree A-V block showing such periodicity,[15,16] prolongation of the A-V interval in the second conducted beat from 120 to 160 msec. results predominantly from an increased intranodal delay, as shown by a prolongation of SA-NH interval from 82 to 110 msec. (intra-atrial conduction time at this point was 25 msec.). However, a smaller additional conduction delay is seen below this NH fiber with the His-Purkinje conduction time increasing from 38 to 50 msec. The explanation for this additional delay in the absence of intraventricular conduction dis-

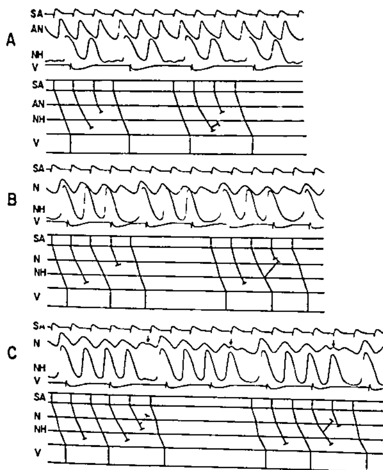


Fig 8 *A B* and *C* Various A V conduction ratios during rapid atrial stimulation (300 per minute) Transmembrane potentials of AN region (*AN*) or N region (*N*) are recorded simultaneously with NH action potentials (*NH*) as well as SA and V electrograms Sequence of A V transmission with possible re entry is illustrated in the diagrams See text for detailed discussion.

may reach such a point that numerous atrial impulses are blocked consecutively Fig 7 shows such an example In the initial portion of this continuous record two cycles of 2 1 conduction are seen Marked step-formation preceding a more rapid depolarization of this N fiber in conducted beats may again suggest decremental conduction or inhomogeneous conduction [22] This period is then followed by successive block of twelve atrial impulses within the A V node Finally the thirteenth impulse produces depolarization of the N fiber with a less marked step formation and is successfully conducted to the ventricles A period of 2 1 conduction is then re established

It must be pointed out that in similar experimental as well as clinical records showing prolonged periods of ventricular asystole depressed automaticity in the A V transmission system distal to the site of block is probably present in addition to the conduction abnormality Otherwise escape of a subsidiary pacemaker will prevent the appearance of 3 1 4 1 or higher conduction ratios

II A V block during rapid atrial rhythm It is well known that atrial flutter in man usually shows a rate of approximately 300 per minute and is most commonly associated with a 2 1 A V conduction The next most common conduction ratio appears to be 4 1 while any odd numbered conduction ratios are said to be rarer and are suggestive of an underlying conduction disorder When atrial flutter was simulated in isolated rabbit hearts by electrically

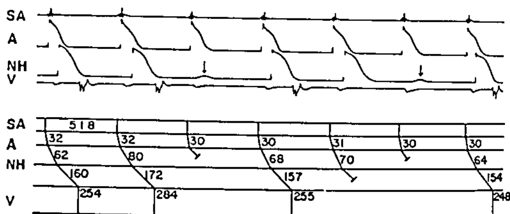


Fig 6 Same experiment as shown in Fig 1 Transmembrane potentials from a perinodal atrial fiber (*A*) and an NH fiber (*NH*) are recorded together with S A nodal (*S A*) and ventricular (*V*) electrograms Arrows indicate non propagated local responses in the NH region Periods of 3 2 and 3 1 A V conduction alternate Detailed discussion in text

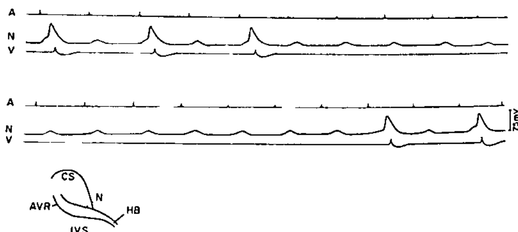


Fig 7 Intranodal concealment of multiple consecutive atrial impulses Transmembrane record from an N fiber (*N*) with atrial (*A*) and ventricular (*V*) electrograms is shown Inset shows a schematic diagram of the A V junctional area *CS* = ostium of coronary sinus AVR = fibrous atrioventricular ring HB = His bundle IVS = interventricular septum

short and long P R intervals during regular 2 1 A V block Since the QRS is not widened and intraventricular conduction appears normal in contrast to the example shown in Fig 2 both of the two levels of concealment postulated in every other (blocked) beats must be located above the bifurcation of the His bundle most likely within the A V node Hence this ECG is analogous to the experimental record shown in the left half of Fig 3 (*A* and *B*) Further more, periods of 3 2 and 4 2 A V conduction seen in Leads II and III of Fig 5 are similar to those shown in Fig 4 *A* and *B* re spectively

In contrast to a 3 1 A V conduction re sulting from intranodal block (Figs 3 and 4), a 3 1 response due to two distinctly different levels of block is illustrated in Fig 6 (right half), where the first non conducted atrial impulse is blocked below the distal NH region and probably within the His Purkinje system while the second non conducted impulse is blocked above the NH region This period of 3 1 response followed a period of 3 2 conduction This record was obtained from the same experi ment as shown in Fig 1 Thus, intraven tricular conduction disturbance is evi denced by a prolonged His Purkinje con duction time and a widened ventricular electrogram It must be pointed out that combined intranodal and His Purkinje block could cause (1) regular 2 1 A V conduction with fixed or alternating A V intervals (2) 3 2 conduction and (3) 3 1 conduction varieties quite similar to those produced by different levels of concealment within the A V node alone (Figs 3 and 4)

Sometimes A V conduction disturbance

cessive cycles and is accompanied by a gradual decrease in the action potential amplitude This is a common *finding in intranodal conduction block with Wencke*bach phenomenon and is considered an expression of decremental conduction [15 21] However on closer observation the fourth (the smallest) action *potential of the N* fiber occurs slightly earlier than is expected from the preceding sequence of depolarization Two alternative explanations for this finding are (1) forward transmission *of the* atrial impulse *with a shorter* SA N conduction *time (Fig 8* diagram at left) and (2) retrograde activation of the N fiber by a re-entrant impulse probably from the NH region (Fig 8 diagram at right) Since a sudden acceleration of forward conduction after *an apparent* increase in decrement is not readily explained the second mechanism suggested above seems more plausible. A greater action *potential amplitude* accompanied by an increased rate of depolarization in the subsequent (fifth) N potential may possibly be a result of slightly longer cycle length

In Fig 8 *C* the ventricular electrogram again shows an *alternation* of short and long cycles *This* time however the sum of short and long cycles equals five atrial intervals instead of four as seen in *B* The sequence of activation *in the N and NH* regions and the ventricles suggests alternating 2 1 and 3 1 A V conduction ratios (see diagrams) The period of 2 1 conduction *is quite* similar to the first cycle of 2 1 response in Fig 8 *B* in that *the non* conducted impulse *is blocked* below the NH region (*deeper penetration*) The third atrial impulse is therefore conducted to the ventricles with a prolonged A V interval In contrast to the sequence seen in *B* the fourth atrial impulse again *penetrates* deep into (or beyond) the NH region and is blocked within *the His* Purkinje system This is followed by block of the fifth impulse above the NH fiber resulting in a 3 1 conduction ratio Such transition *from* 2 1 to 3 1 conduction closely *resembles* that in Fig 3 *B* recorded *in* the presence of a slower atrial rhythm

The transmembrane potential from the N fiber again suggests a progressively increasing decrement in five successive depolarizations with the sixth *action* potential showing a greater amplitude and a more rapid phase O depolarization Three groups of five *action potentials are thus shown in* this figure as compared to the groups of four N potentials in Fig 3 *B* In this instance however either the fifth (in the first group) *or the fourth (in the second and third group) N* potential of a group shows a distinct notch or doubly peaked appearance (arrow) The most *likely* explanation *for this finding is* a *re entry movement from the area distal* to this N fiber as illustrated in the diagram When the fourth action potential is doubly peaked (diagram at right) the fifth *potential shows* a further reduction *in the amplitude* and the rate of *depolarization* but without a notch The NH recording then shows no signs of electrotonic spread *following the* fourth *action potential* Thus the fifth atrial *impulse here appears blocked* immediately distal to this N fiber When the fifth N potential has double peaks on the other hand there is a small local *response of the NH fiber after its fourth* action potential (asterisk) A slightly deeper penetration of the fifth atrial impulse possibly due to the absence of re entry of the preceding impulse may have caused deeper penetration and *reciprocation* of this impulse (diagram at left) However this interpretation may impose some difficulty in explaining the better N potential seen in the subsequent (sixth) *depolarization since the* period for *recovery in this fiber* apparently *is even shorter* than in the preceding cycles Possible mechanisms for such findings will be discussed later

Nevertheless these observ*ations indicate* that the *sequence of concealment* in these *various conduction* ratios is essentially identical in the presence of both slow and more rapid atrial mechanisms although the actual levels of block may be *different* in individual cases Furthermore it is interesting to *note* the relationship between *grouping of* NH action potentials and A V conduction ratio during the simulated atrial flutter When the NH *recording* shows grouping of two *action potentials* a 3 1 *conduction may result* grouping of three *action* potentials could cause a 2 1 *conduction* with alternating short and long A V intervals and grouping of *four action* potentials is associated with alternation of

stimulating the right atrium at similar frequencies 2:1 A-V block commonly appeared. In such instances every other atrial impulse was usually blocked within the A-V node causing a 2:1 response in the distal NH region (not shown). Fig. 8 illustrates less common varieties of conduction observed in one of these experiments.

In Fig. 8,*A* the atrial electrogram recorded from the S-A nodal region reveals a rate of 300 per minute while the ventricular electrogram shows a rate of 100 per minute indicating a 3:1 A-V conduction. The presence of 1:1 response in the AN (atrionodal) region is clearly seen in the intracellular record designated *AN*, although a decrease in the rate of phase O depolarization is apparent. On the other hand the transmembrane potentials recorded from an NH fiber show two propagated action potentials followed by a pause. The first NH potential appears relatively normal in configuration, and is accompanied by ventricular excitation. There is an increased delay between activation of the AN and NH fibers in transmission of the second atrial impulse. The second NH action potential starts from a lower membrane potential and shows a markedly reduced rate of depolarization, probably due to incomplete recovery of excitability in this region. This impulse is then blocked below this NH fiber and ventricular excitation does not follow. Such failure of subnodal propagation may have resulted from a reduced efficacy of these NH action potentials in exciting the immediately distal AV transmission system or the His bundle. It is well known that any cause which reduces the action potential amplitude and the rate of phase O depolarization could produce a decreased conduction velocity and decrement.[23] Thus, the level of block of this second impulse most probably is in the main His bundle. An alternative explanation is that, due to a lower frequency of "effective" impulses invading the His-Purkinje system (100 per minute) the duration of action potential and refractory period in the His-Purkinje fibers during successful transmission of the first atrial impulse is prolonged causing a refractory barrier to the second impulse below the NH region.

In contrast the third atrial impulse is blocked above this NH fiber, possibly because of a progressively increasing decrement within the A-V node as commonly seen in Wenckebach type of second degree block.[15] Hence 3:1 A-V conduction in this instance is associated with a deeper penetration of the first and a less deep penetration of the second non-conducted impulse. This sequence is similar to that seen in Fig. 6 although the levels of concealment might be different. The small undulations seen following the second NH action potential are probably electrotonic spread from either forward penetration of the third atrial impulse or an attempted reciprocation (re-entry) of the second impulse below this NH fiber, or both (see diagrams below Fig. 8-*A*).

Fig. 8, *B* and *C*, are different portions of a long continuous record obtained 15 minutes prior to the recording of *A*. Transmembrane potentials are recorded from an N fiber and an NH fiber slightly more distal to the NH fiber in Fig. 8-*A*. Inspection of the ventricular electrogram in *B* reveals an alternation of long and short cycles the sum of which corresponds to four atrial intervals. Transmembrane action potentials from the N fiber show an apparent 1:1 response to the atrial impulses while a group of three NH potentials is regularly followed by a pause. A progressively increasing conduction delay appears to be present between the N and NH fibers, although the onset of depolarization cannot be precisely determined in these slowly rising action potentials. The sequence of A-V conduction is interpreted as shown in the diagram, i.e., a 2:1 conduction with alternating short and long A-V conduction time. This is quite similar to the observations made in the presence of a slower atrial rhythm (Fig. 1*B*) since a longer A-V interval follows a blocked impulse with deeper penetration (to or beyond the distal NH region) while a shorter A-V interval follows the block of an impulse at a higher level (above the NH region). In both instances groups of three propagated responses are seen in the distal NH region.

Although every atrial depolarization appears to be followed by an action potential in the N fiber the rate of phase O depolarization is progressively decreased in four suc-

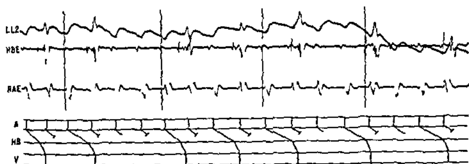


Fig 10 Simultaneous recordings of the standard Lead II (*LL2*) His bundle electrogram (*HBE*) and right atrial electrogram (*RAE*) in a patient with atrial flutter and varying conduction ratios similar to Fig 9 *B* The ladder diagram shows period of 2 1 4 1 and 3 1 A V conduction Note that every QRS complex is preceded by a His deflection with essentially identical H Q interval but no His potential is seen following a right atrial excitation that is not conducted to the ventricles Some of the oblique lines representing concealed conduction are dotted as the depths of penetration cannot be judged from the His bundle recording

atrial and ventricular excitation is available the designation of upper and lower A V junction may be somewhat misleading Today when His bundle electrograms are available the A V transmission system may be conveniently divided into the portions above and below the His bundle recording site which may enable us to identify different sites of conduction disturbance in certain selected cases However it must be stressed that many theoretical deductions made from the ECG analyses alone have previously been confirmed by various investigators particularly with the use of premature stimulation or other experimental conditions favoring the occurrence of concealed conduction [8,14]

On the other hand several examples of second degree A V block with different and sometimes multiple levels of delay and propagation failure have been reported from our laboratory [3,16] Other less common varieties of A V block discussed in the present study further illustrate multiple levels of concealment in the A V transmission system For instance Figs 1 and 6 clearly indicate that when an intraventricular conduction disturbance is present two levels of block can develop one within and the other below the A V node It is therefore reasonable to assume that a clinical tracing as shown in Fig 2 resulted from a combination of intranodal and His Purkinje block In contrast multiple levels of block could develop entirely within the A V node in the presence of normal intraventricular conduction (Figs 3 and 4) In these instances depths of intranodal penetration may be judged from the size of local responses [13,22] Hence when two levels of concealment are postulated in an ECG showing normal QRS complexes (Fig 5) conduction disturbance is most probably confined within the A V node but showing variation in the depths of penetration

Another variety of two levels of concealment in the presence of normal intraventricular conduction involves block within the A V node and that below—probably in the main His bundle (Fig 8) When an impulse decrements sufficiently within the A V node but is still capable of traversing the critical N region the resultant action potential in the NH region may show a decreased amplitude and rate of depolarization Such NH potentials may be inefficient to fully activate the His bundle resulting in failure of propagation within this latter structure Here again however an increased decrement in the A V node appears to play a major role

The effects of refractoriness in the more distal regions of the A V conduction system in preventing propagation of some impulses which traversed the A V node have been pointed out with reference to Fig 8 1 Once the number of impulses reaching subnodal regions is reduced due to the development of second degree intranodal block resultant longer cycle lengths could cause a prolongation of the refractory period in fibers of the His Purkinje system and blockage of the immediately succeeding atrial impulse particularly when atrial rate is rapid as in flutter This mechanism may explain formation of an additional

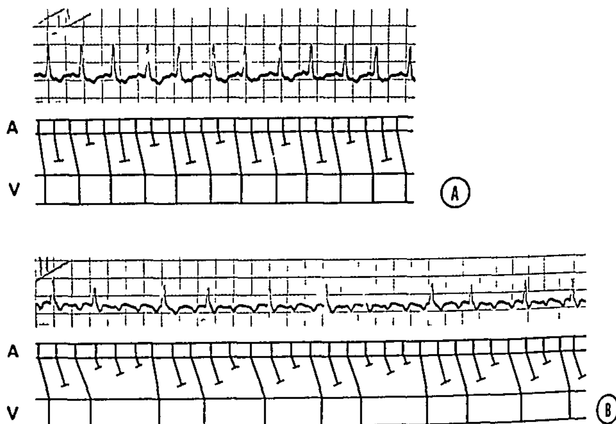


Fig 9 A and B Electrocardiograms (Lead II) from two patients with atrial flutter Regular 2 1 A V transmission with alternation of short and long A V intervals (*A*) and varying conduction ratios ranging from 2 1 to 4 1 (*B*) are shown

2 1 and 3 1 conduction ratios (Fig 8 *A* B and *C* respectively) It is conceivable that, when conductivity in the subnodal region is more normal these groupings of NII action potentials may result in 3 2 4 3, and 5 4 A V conduction ratios In the latter case, there will be only one level of concealment

Fig 9 illustrates clinical examples of atrial flutter with these several conduction ratios In *A* a Lead II electrocardiogram shows regular undulations of the baseline at the rate of 320 per minute indicating flutter There is alternating short and long ventricular cycles with an average ventricular rate of 160 per minute This must be interpreted as 2 1 A V conduction with alternation of deeper and less deep penetration of the non conducted atrial impulses a clinical counterpart of what was shown in Fig 8 *B* In part *B* of Fig 9 a Lead II recorded from a different patient, A V conduction ratios ranging from 2 1 to 4 1 are seen as diagrammed below Various sequences of partial penetration in this tracing may well be considered similar to those seen in Fig 8, *A* and *C* In these clinical cases of atrial flutter, however it cannot readily be determined whether those impulses penetrating deeper into the A V junction did partially invade the His bundle or were blocked within the NH region A *His* bundle electrogram recorded in a similar patient (Fig 10) failed to supply such information

That multiple levels of concealment are also seen in retrograde transmission in the presence of so called ventricular tachycardia has previously been reported [18]

Discussion

In his original article on concealed conduction Langendorf[6] already postulated different depths of penetration into A V junction of the blocked impulses in order to explain variation of the subsequent P R interval Later, two levels of concealment were often referred to as "upper and lower portions of the A V junction especially in the presence of A V junctional impulse formation or atrial flutter [7,24] Although such arbitrary subdivision of the A V transmission system is inevitable in clinical electrocardiography where only information on

non-conducted impulse Such sequence of concealment has indeed been observed on several occasions where the first non conducted impulse was blocked in the His-Purkinje system (Fig 6 and Fig 8 1) or blocked within the A V node (Fig 3 *B*) *However other records with intranodal* block showed an opposite sequence or a deeper penetration of the second noncon ducted impulse than the first (Fig 4 *A* and Fig 6 in reference 15) This indicates that the concept of concealed conduction simply leaving the state of refractorines in its wake *may not adequately explain all* similar conduction ratios Furthermore, when a *transition from 2 1 conduction with* alternating short and long P R interval to 3 1 conduction was observed in a clinical example (Fig 8 in reference 7) a 3 1 ratio followed a shorter P R interval In con trast in our Fig 3 *B* the period of 3 1 conduction followed a longer A V conduc tion time of the alternating intervals Even those rare instances of 4 2 A V conduction were associated with either *progressive* prolongation (Fig 4 *B*) or with shortening (unpublished observation) of the A V in terval prior to the blockage of two succes sive impulses

Although these contrasting patterns of conduction may appear insignificant they bring into sharp focus the complexity of abnormal A V conduction It further em phasizes the fact that a more universal explanation is needed for the many varieties of A V block by incorporating numerous mutually interrelated mechanisms rather than what was originally implied by con cealed conduction [6,7] *Since a detailed dis cussion* of all these mechanisms is beyond the scope of this paper and will be pre sented elsewhere [25] only several factors pertinent to the present study are dis cussed

It is well known that the A V conducting system comprises a series of fiber types having different electrophysiological prop erties. For example the atrial A V nodal and His-Purkinje fibers show marked dif ferences in their action potential charac teristics and in their response to the same physiological or pharmacological fac tors Furthermore *any change in the* excitation process occuring in proximal fibers would alter the strength of stimuli and thus indirectly affect depolarization of distal fibers Several investigators showed that both the direction and strength of the excitation front could affect A V nodal transmission [21,23] This is partly explained by the anatomy of A V nodal tissues where *a marked variability* in diameter and length of fibers exists with a complex network [24] Within this net like structure of the A V node transmission of impulses is further complicated by local differences in excit ability particularly under abnormal con ditions This could result in an irregular *fragmented excitation front* which is less effective in exciting the more distal tissue Such inhomogeneous conduction within the A V node culminating in unidirectional block and re entry of an impulse was re ported earlier [12] Similar findings were later reported by other investigators utilizing premature atrial stimulation [25] Once re entry occurs in the A V junctional tissue it would possibly leave non uniform areas of refractoriness or excitability affecting *the wave front* of subsequent impulses Depending on the location and extent of the re-entry movement and also on the presence or absence of areas participating neither in forward nor in retrograde trans mission (bidirectional block) the succeed ing wave of excitation may become either more fragmented or reorganized Thus conduction is further depressed in some instances while it is improved in others This may explain the apparent paradox of 3 1 conduction with progressively deeper penetration of the two blocked impulses (Fig 4 *A* and Fig 6 reference 15) in contrast to successively less deep penetra tion in 3 1 conduction (Fig 3 *B*) Further more the observation of a better action potential immediately following an ap parent re-entry movement (Fig 8 *C* sixth N potential in the left diagram) may be explained by this concept

In addition to inhomogeneity of conduc tion temporal fluctuations of conductivity must also be considered *In any depressed* tissue with reduced membrane potential and decreased rate of phase O depolarization (especially in the N region of the A V node) the safety factor for conduction may be *marginal* Hence it is possible that with only minor variations in coronary flow and oxygen supply [21,26] vagal tone [27,28] or other

level of conduction block below the A V node, when no underlying intraventricular conduction disturbance is present. Such interpretation may be supported by the fact that (1) the action potential duration becomes progressively prolonged from the atrial fibers through the A V node[4] and down to the peripheral Purkinje fibers[3] and (2) the effects of altered cycle lengths on the action potential duration are most pronounced in the Purkinje system.[26,27] Concealment of some impulses within the right bundle branch system resulted from this mechanism, when several premature atrial stimuli were applied in rapid succession.[11]

Operation of a similar mechanism may also be invoked in the presence of a slower atrial rhythm. In Fig. 6, for instance, block of the fifth atrial impulse below the NH region may possibly be explained by a prolonged refractory period in the His Purkinje system due to a long preceding cycle (greater than 1000 msec.) caused by intranodal block of the third impulse. This would imply a prolongation of the effective refractory period to 520 msec. or longer. This marked prolongation may not be common but is seen under certain conditions.[27] If we accept this possibility, maintenance of a regular 2:1 block at the His Purkinje level as seen in Fig. 1 *A* from the same experiment can be explained on the same basis. On the other hand, one might theoretically expect still a longer duration of refractoriness in the His Purkinje system after a period of 3:1 conduction (Fig. 6, right). This should tend to perpetuate a 3:1 response, or at least 2:1. However, 3:1 conduction alternated with a 3:2 conduction for several cycles in the remaining portion of this continuous record. This may suggest operation of mechanisms other than refractoriness. Decremental conduction at the bundle branch level may not be ruled out as a possibility since underlying intraventricular conduction disturbance is evident in this instance.

The role of refractoriness has also been suggested in a different manner in the presence of atrial flutter.[7] Langendorf and Pick[7] postulate that, when the atrial rate is quite rapid (e.g., 300 per minute), every other impulse will arrive at the A V junction during its refractory period and hence is ineffective to excite the junctional tissue. This reduces the number of impulses invading (and usually traversing) the A V junction to one half the flutter rate (150 per minute). If intranodal conduction is now depressed, some of these invading impulses are blocked, often causing a 4:1 response. They term these mechanisms as two levels of "impedance," one at a higher level and due to physiological interference and the other at a lower level due to abnormal conduction block.[7] It is obvious that the term "physiological interference" as used by these authors represents failure of propagation as a result of refractoriness. These authors further argue that in these more common varieties of A V conduction ratios (2:1 and 4:1) during atrial flutter, concealed conduction does not have to be invoked. The following comment appears pertinent regarding the definition of concealed conduction.

According to Langendorf and Pick[7] concealed conduction "consists of incomplete penetration of preformed conduction pathways by an apparently blocked impulse. It manifests itself by its effect upon conduction or formation of a subsequent forward or retrograde impulse." It seems that many electrophysiologists regard the first part of the above statement as the sole criterion for concealed conduction.[8,13] In that case any impulse blocked within the A V transmission system should constitute an example of concealed conduction, whether it manifests itself or not. Strictly speaking, however, no "concealment" exists in electrophysiological studies utilizing microelectrodes, as direct recording of those blocked impulses is possible. Furthermore, the original definition of concealed conduction as quoted above[7] has been widely accepted. Hence, the word "concealed conduction" should be reserved for clinical electrocardiography and should include its manifestation by its effects on conduction or formation of a subsequent impulse, while "partial penetration into the A V transmission system" may be a more acceptable term in electrophysiological studies.

The mechanism of the 3:1 conduction ratio has been explained by a deeper penetration of the first non conducted impulse which produces more refractoriness of the A V junction[7] and thus blocks the second

cycling starts again In other words regular alternation of short and long A V intervals with 2 1 A V response *resulted from this* particular intranodal conduction ratio—i e 4 3

The above explanation is further supported by the finding in Fig 6 a record obtained 4 minutes after Fig 1 *B* Here intranodal conduction is slightly more depressed resulting in a 3 2 conduction ratio Every third atrial impulse is now blocked within the A V node Whether both of the two NH responses could traverse the His Purkinje system may then depend on slight fluctuation of subnodal conductivity or *duration* of refractoriness in Purkinje fibers or both The possible role of the refractory period in this record has already been discussed Thus a 3 2 intranodal conduction results either in 3 2 or 3 1 A V response (Fig 6) Later in this experiment only 2 1 intranodal block was observed indicating further deterioration of the intranodal conduction (not shown) Although this should result in a constant shorter A V interval the expected shortening of conduction time was not apparent because of a progressive depression of conduction throughout *the* A V transmission system It should be re emphasized that a similar relationship between the intranodal conduction ratios (or number of NH responses) and the A V conduction ratios (or number of ventricular responses) was clearly seen in the presence of a rapid atrial mechanism (Fig 8)

Finally the values and limitations of His bundle recordings during A V block may deserve a brief comment If the impulses blocked below the distal NH region in Figs 1 and 6 are conducted through the main His bundle but blocked at the *bundle* branch level His electrograms would yield the same information as obtained in these experimental studies Similarly if those impulses blocked below the NH region in Fig 8 did invade but decremented within the main His bundle as postulated above a His electrogram recorded from an appropriate site may reveal an attenuated deflection suggesting *decremental conduction*[41] In such a case His bundle recordings will be of value in localizing the level of block and in demonstrating the effects of concealed conduction However His bundle electrograms recorded from a similar clinical case (atrial flutter with 2 1 3 1 and 4 1 A V conduction) failed to show any evidence of partial penetration into the His bundle (Fig 10) Therefore whether some of the blocked impulses penetrated deeper or not could not be judged from this recording It should also be pointed out that even when an attenuated His deflection is recorded extreme caution must be exercised to rule out the possibility of temporary catheter displacement before decremental conduction is invoked Furthermore His bundle electrograms would not supply information on the different levels of concealment *within the A V node* (Figs 3 and 4) nor would it reveal any evidence for intranodal re entry (Fig 8) Despite these obvious limitations His bundle recordings would still prove a useful clinical tool in studying certain selected cases of abnormal A V transmission

Summary

Different levels and sequences of propagation failure within the A V transmission system in the presence of second degree and advanced second degree A V block were demonstrated in isolated perfused rabbit hearts utilizing the microelectrode techniques Alternation of short and long A V conduction time during a regular 2 1 A V block was shown to result from alternation in the depths of penetration of non conducted impulses into the A V junctional tissues A 3 1 A V conduction ratio resulted either from (1) subnodal block of the first non conducted impulse followed by intranodal block of the second non-conducted impulse or (2) intranodal block of two consecutive impulses with either deeper *or less deep penetration of the first* non conducted impulse as contrasted to the second The first variety was observed either with wide QRS complexes (disturbed intraventricular conduction) or with normal QRS duration (normal intraventricular conduction) while the second variety was associated with normal intraventricular conduction Transition between various conduction ratios including 2 1 3 1 4 1 3 2 and 4 2 was observed and multiple intranodal concealment was also demonstrated Similarities of the sequence of partial penetration in both slower sinus

physiological factors, propagation of impulses may fail at one moment but may barely succeed at the next It will be readily understood that combination of these two factors (spatial inhomogeneity and temporal fluctuations of conductivity) could produce any sequence and ratio of conduction Thus, such a term as "abortive attempt at 2 1 and 3 2 conduction"[7, 1] may have a practical value in describing certain conduction phenomena, but may not reveal the precise physiological mechanisms

On the other hand, some comment is necessary regarding the so called dual A V transmission system The early physiological observations suggesting the presence of two functional pathways[39] were subsequently explained by interactions between intranodal conduction time and recovery of excitability in the His Purkinje system,[40] and therefore may not be pertinent in the present discussion However, a similar concept may still be applicable in certain conduction phenomena as shown in Figs 1 and 2 One of the explanations of Fig 2 given by Katz and Pick[21] invokes two pathways with different conduction velocities When impulses are transmitted through the two pathways alternately an alternation of short and long P R intervals will result while transmission through only one of the pathways will cause a constant (either long or short) P R interval If we assume that such dual pathways are located entirely within the A V nodal tissue alternation of short and long P R intervals must necessarily be accompanied by an alternation of short and long intranodal conduction times with essentially no change in subnodal (His Purkinje) conduction Assumption of dual pathways located below the A V node would result in an opposite sequence of events Our experimental observations in Fig 1, however do not confirm these explanations During alternation of short and long A V intervals (Fig 1 *B*) there was a progressive prolongation of intranodal conduction time in the form of Wenckebach periodicity, causing a 4 3 response in the distal NH region Intranodal block of an impulse was followed by a shortening of both intranodal and His Purkinje conduction time Furthermore the period of 2 1 conduction with a fixed long A V interval (Fig 1 *A*) was associated with a short (not long) intranodal conduction time but always with a deep penetration of the blocked atrial impulses into subnodal regions A little later in the same experiment, periods of 3 2 and 3 1 A V conduction were observed (Fig 6), with a still longer A V conduction time during a 3 2 ratio Similar conduction phenomena in the presence of intranodal block alone were also associated with alternation of the depths of penetration (Fig 3) Thus, at least in these particular experiments, no evidence of dual A V pathways was suggested Hence, different depths of penetration due to fluctuations of conductivity as discussed above appears the most plausible explanation A similar statement was originally made by Katz and Pick[1]

Regarding the transition from Fig 1 *A* to Fig 1 *B*, the following interpretation may be proposed Although conduction was depressed in both the A V node and the His Purkinje system transmission of impulses was more critical in the latter tissue initially The A V node was still capable of 1 1 transmission as seen in action potentials from the NH fiber If a single impulse fails to be propagated below the NH region, perhaps due to slight fluctuations in conductivity, a resultant longer interval below the site of block may prolong the duration of action potential and refractoriness in His Purkinje fibers When such prolongation reaches a value similar to the atrial cycle length, an impulse following upon a conducted beat may encounter such a refractory barrier and be blocked again subnodally This sequence would tend to sustain periods of 2 1 conduction at the His Purkinje level (Fig 1,*A*) Subnodal conduction time remains prolonged partly as a result of repeated partial penetration of the His Purkinje system by non conducted impulses Subsequently intranodal conduction becomes further depressed and a Wenckebach phenomenon with eventual failure of propagation develops When intranodal conduction shows a 4 3 response as in Fig 1,*B* every fourth impulse is blocked within the A V node instead of the His Purkinje system while every second impulse is still blocked subnodally Following block of an impulse within the A V node shortening of conduction time occurs both within and below the node and this

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entered the wall and on the other hand that which has been disposed of by the wall Comparatively few studies have been aimed to determine the mechanisms and the capacity of the arterial wall to dispose of this accumulation of cholesterol and cholesterol compounds attributes which play a part in preventing excessive lipid accumulation in the arterial wall Murphy[8] has demonstrated the presence of an equilibrium between free cholesterol of the serum and that of the red blood cells and has shown that the flux of free cholesterol from the cells to the serum increases as the serum cholesterol becomes esterified during incubation If a similar type of equilibrium exists between free cholesterol of the plasma and that of the arterial tissue then a decrease in cholesterol esterification in plasma might be important in the rate of development of atherosclerosis This study was undertaken to determine whether such a decrease exists in patients with clinically manifest atherosclerosis of the coronary arteries

Subjects and methods

Sixty subjects were studied The first group consisted of 12 patients with acute myocardial infarction documented by a characteristic history physical examination electrocardiographic (ECG) features and changes in serum enzymes. There were 11 men and 1 woman ranging in age from 35 to 73 years with a mean age of 57 years A second group included 16 patients with coronary artery disease in its chronic stages but free of acute myocardial infarction The diagnosis was confirmed by the characteristic ECG evidence of old myocardial infarction and by the presence of significant arterial obstruction as revealed by coronary cineangiography There were 15 men and 1 woman ranging in age from 37 to 70 years with a mean age of 56 years The control group for the present study consisted of 12 men subjects 36 to 65 years old with a mean age of 55 years Nine of these men have been physicians on the staff at Temple University Health Sciences Center for many years and one of us (LAS) has known them for at least 25 years or more during which time they have been examined periodically for pre insurance physical examinations and occasionally for an annual physical examination as part of a Temple University service for its alumni All of these men have been in excellent health over the years and have never had symptoms referable to heart disease They are extremely active and engage in sports such as skiing handball squash swimming golf and fishing Physical examination of the cardiovascular system of these subjects has always been normal Cardiac size by roentgen ray study of the chest and ECG s were always normal and the family history of this group has been remarkably free of any premature atherosclerosis and coronary artery disease The other three healthy subjects were chosen for the following reasons two were seen for routine physical examination Their present and past history was negative for cardiovascular disease Physical examination and roentgen ray studies of their chests were normal Their ECG s and two step Master tests were normal and they had family histories of marked longevity The third subject had been referred because of vague chest distress occurring intermittently for several months He and his physician desired coronary arteriography to exclude coronary artery disease and this study was normal A second younger control group composed of 20 young healthy volunteers (medical students house officers and laboratory technicians) who were free from familial tendency toward premature atherosclerosis was also studied There were 15 men and five women 25 to 32 years old with a mean age of 27 years

Blood samples were collected directly into glass tubes with no preservatives added from each of the subjects after an overnight fast All hemolyzed specimens were discarded In those patients with acute myocardial infarction specimens were drawn within the first 48 hours after admission into the hospital Usually two and never more than three subjects were studied in one day and all incubation studies were begun on the day of collection of blood Studies on healthy subjects and on patients with coronary artery disease were scattered throughout the time of the investigation All collected blood samples were placed immediately in ice allowed to clot and transported at once to the laboratory where they were centrifuged immedi

In vitro serum cholesterol esterification in coronary artery disease

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Sperry[1] was the first to demonstrate *in vitro* esterification of cholesterol He reported that incubation of human serum and plasma at 37° C for three days resulted in a marked decrease in free cholesterol with no change in total cholesterol Le Breton and Pantaléon[2] demonstrated the participation of serum lecithin in the plasma cholesterol esterification reaction Glomset and his associates[3,4] have studied this reaction in detail and recently Glomset[5] reviewed the literature In essence during incubation of plasma cholesterol esters are formed in the plasma by the action of lecithin cholesterol acyltransferase (LCAT) which appears to react preferentially with high density lipoproteins to catalyze the transfer of fatty acids from the 2 position of lecithin to the hydroxyl group of free cholesterol The esterified cholesterol is subsequently transferred in part to the very low density lipoproteins[6] On the other hand Schumaker and Adams[7] have suggested the possibility that the primary function of LCAT is related to maintenance of lipoprotein structure They have proposed that as triglyceride is removed from the lipoprotein by the action of lipoprotein lipase LCAT causes a concomitant reduction in the lipoprotein surface by the removal of 1 1 units of lecithin and free cholesterol thus enabling the lipoproteins to retain spherical shape and similar surface properties Although other cholesterol esterifying systems may be present in plasma, *in vitro* cholesterol esterification has been used as one measure of LCAT activity[5]

The arterial wall contains variable amounts of cholesterol cholesterol esters, and phospholipids the total amount representing a balance between on the one hand that which has been synthesized or has

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Table II Triglyceride and cholesterol concentration in mg per 100 ml—data for 12 age matched controls

Age matched controls	Age	Sex	Triglycerides	T C	F C†	F C† after incubation (hrs) 3	6	24	48
M N	49	M	44	202	51	46	40	20	24
M R	53	M	210	210	47	46	40	23	21
H B	52	M	194	211	67	55	47	30	23
G B	65	M	215	212	67	53	44	29	21
J H	55	M	64	220	54	47	43	33	27
H K	50	M	159	220	56	45	37	24	18
N P	61	M	157	256	74	67	60	41	32
W L	49	M	347	260	78	68	56	35	26
L S	65	M	87	282	86	72	60	55	35
I G	64	M	54	292	69	62	61	44	39
H S	56	M	54	310	83	73	67	49	49
J K	36	M	173	320	92	82	55	43	41

*T C = total cholesterol
†F C = free cholesterol

with the Michael Reese value with 99 per cent accuracy The normal range given by that laboratory was 30 to 110 mg per cent at the time this study was done but its normal range has since been established at 30 to 135 mg per cent

The clinical status of each of the patients with acute myocardial infarction is included and it should be noted that although many had transient arrhythmias and three had mild to moderate congestive heart failure none had any signs of shock or pulmonary edema within the first 48 hours of admission the time period in which blood was drawn for these studies Three of the patients ultimately had stormy hospital courses but all were eventually discharged from the hospital

Results

Tables I to IV show the changes in serum free cholesterol after incubation at 37 C for 3 6 24 and 48 hours for all subjects in the study Table V reveals the mean data for each of the four groups studied with comparisons between the groups for total and free cholesterol and cholesterol esterification at 3 6 24 and 48 hours It should be noted that both total and free cholesterol concentrations were significantly lower in the young controls a finding which makes comparisons of esterification somewhat difficult In addition although not significantly different the mean total cholesterol concentrations in subjects with acute myocardial infarction was 15 mg per 100 ml higher than that of the age matched healthy controls Nevertheless the serum free cholesterol concentration prior to any incubation was significantly higher in those subjects with acute myocardial infarction compared to the age matched healthy controls ($p < 0.05$) The comparison of subjects with chronic coronary artery disease with the age matched controls where both total and free cholesterol concentrations were similar revealed significantly decreased esterification ($p < 0.05$) after 6 24 and 48 hours incubation

The data were then analyzed from another perspective This was considered because of reports in the literature suggesting a tendency for *in vitro* cholesterol esterification to be higher at hypercholesterolemic concentration[11 12] There were nine subjects in the study with total serum cholesterol concentrations > 300 mg per 100 ml Four of these presented with chronic coronary artery disease three with acute myocardial infarction and two were age matched controls This group of subjects was separated and the average slope which

Table I. Triglyceride and cholesterol concentration in mg. per 100 ml.—data for 20 young control subjects

Young controls	Age	Sex	Triglycerides	T.C.*	F.C.†	F.C.† after incubation (hrs.)			
						3	6	24	48
F. C.	25	M	59	161	47	43	41	25	20
S. I.	26	F	23	171	60	56	48	32	29
J. B.	24	M	47	172	43	38	50	18	14
S. M.	29	M	25	176	39	32	50	18	17
W. H.	25	M	74	190	57	45	40	22	20
I. S.	25	F	56	196	55	54	43	24	18
W. J.	30	M	47	197	46	40	34	23	18
N. B.	24	M	47	198	62	56	58	35	35
J. A.	28	F	39	209	62	54	47	35	31
I. M.	30	M	50	209	61	56	55	40	36
R. T.	24	M	110	211	66	58	53	39	36
H. N.	30	M	38	223	67	54	47	31	29
B. H.	27	M	70	226	48	40	31	15	13
J. P.	32	M	168	232	77	71	43	32	24
P. W.	24	M	72	233	58	50	47	28	24
F. V.	30	M	118	251	64	54	46	34	29
A. K.	26	M	62	252	55	52	52	37	28
M. N.	23	M	22	256	83	78	40	45	47
C. K.	24	M	90	260	78	70	58	47	43
I. B.	32	F	72	261	69	51	44	25	23

*T.C. = total cholesterol.
†F.C. = free cholesterol.

ately at 3,000 × g for 15 minutes at 4° C. and the serum was divided into two aliquots. Lipid extraction (acetone-ethanol V/V mixture) was immediately added to the first of these aliquots which was to serve as the pre-incubation control. The second serum aliquot was placed in a 15 ml. disposable sterile test tube and the tube incubated in a water bath at 37° C. Two ml. samples of serum were removed by sterile pipettes after 3, 6, 24, and 48 hours of incubation and 0.5 ml. of the serum samples immediately pipetted into the extraction mixture. All determinations were done in triplicate. Serum total and free cholesterol concentrations were determined on all of the samples using the method of Zak and associates.[9] Since the total cholesterol at all incubation times remained relatively constant within the 1 to 2 per cent variation in this method, the decreases in free cholesterol concentrations observed after the various incubations were used as a measure of cholesterol esterification and expressed as mg. of free cholesterol esterified per 100 ml. of serum. All chemical determinations were performed in the Research Lipid Laboratory and all samples were handled by the same two research technicians who would work simultaneously on each sample (if two subjects were studied) so that there could be no difference in incubation times. If three subjects were studied on one day, addition of the extraction mixture to the third sample was prolonged at most by one minute. All samples for each of the incubation times were then stored at 4° C. and kept until the final incubation time so that all of the samples for a particular subject would be analyzed at the same time.

Serum triglycerides were analyzed by a slight modification of the method described by Carlson[10] as performed by the Lipid Standardization Laboratory of the Communicable Disease Center in Atlanta, Georgia. Standards were supplied by the Michael Reese Research Foundation in Chicago and determination of triglycerides in these standards by our technic correlated

Table IV Triglyceride and cholesterol concentration in mg per 100 ml—data for 16 subjects with chronic coronary artery disease

Chronic CAD‡	Age	Sex	Triglycerides	T C	F C†	F C† after incubation (hrs)			
						3	6	24	48
E. F	50	M	113	195	59	50	44	36	29
H K.	56	M	—	198	61	54	52	40	32
L. K.	46	M	—	201	67	63	58	41	35
M G	62	M	—	214	66	54	51	46	39
G M	70	M	93	218	61	56	55	40	36
A. L.	69	M	59	220	70	65	59	42	41
A. M	37	M	48	229	62	59	59	57	46
W S	56	M	52	242	84	79	73	60	56
H S	61	M	59	247	61	56	54	50	40
J K.	54	M	152	253	72	62	58	44	37
S. K.	63	M	70	253	65	57	57	38	32
H W	57	M	—	278	86	80	74	66	65
M M	49	M	106	312	96	81	77	60	54
J B	57	M	62	322	93	83	77	58	51
L. B	53	M	212	322	83	70	65	47	38
M F	58	M	127	340	111	96	90	70	66

T C. total cholesterol.
F C. = free cholesterol.
‡CAD = coronary artery disease

matched healthy controls slightly above those subjects with coronary artery disease The mean esterification was significantly decreased at six hours in those subjects with acute and chronic coronary artery disease when compared to age matched healthy controls This decrease in esterification in subjects with coronary artery disease was even more significant ($p < 0.01$) at 48 hours compared to the age matched healthy controls At 24 hours there was a significant decrease in the esterification of only those subjects with chronic coronary artery disease compared to the age matched healthy controls There were no significant differences in esterification between all groups at 3 hours although the differences were in the direction of those noted to be significant at subsequent times

There were no significant differences in esterification between the younger controls and the older age matched healthy control group although the mean absolute values for esterification were always higher in the older normal individuals The mean free cholesterol concentration prior to incubation was highest in subjects with acute myocardial infarction This value differed significantly ($p < 0.05$) from the mean value of the young controls but did not differ significantly from the mean value for the age matched healthy controls despite the lower absolute mean free cholesterol concentration in the latter group

It was noted that the trend of the average free cholesterol appeared to be linear with log time from 3 to 48 hours Since the values for each individual over time were correlated it was not possible to use the standard regression method to analyze the differences among the slopes for the three groups However it was possible to compute a slope for each individual within each group and then use an analysis of variance technique[13,14] on the computed slopes to assess statistical differences among the average slopes The pooled within group variation of the slopes was used as the estimate of error This method is equivalent to testing if the average linear trend differed among the groups Fig 2 shows a comparison of these average slopes for the four groups with the mean total cholesterol concentrations held constant as indicated above The slopes of both the acute and chronic coronary artery disease subjects

Table III Triglyceride and cholesterol concentration in mg per 100 ml—data for 12 subjects with acute myocardial infarction

Acute myocardial infarction	*Age*	*Sex*	*Triglycerides*	*T C**	*F C†*	*F C† after incubation (hrs)*				*Clinical status*
						3	*6*	*24*	*48*	
L F	35	M		194	64	55	47	33	24	Uncomplicated course
M C	54	M	145	201	62	53	52	30	28	Frequent PVC‡ and PAC Otherwise uncomplicated course
G E	72	M	100	211	79	75	65	51	55	Sinus bradycardia with escape A V junctional rhythm occas PVC mild CHF 1st and 2nd day
M K	64	M	54	225	68	60	64	62	48	Sinus bradycardia shifting atrial and A V junctional pacemaker
L L	73	M	55	226	68	57	59	44	41	Transient short episodes of atrial flutter and fibrillation
A R	70	M	72	228	61	61	64	—	52	1st degree heart block and freq PVC occas in sequence for first 2 days. Two episodes of recurrent chest pain with vent tachycardia on 6th hospital day
S S	45	M	191	236	76	62	53	48	44	Pericardial friction rub 2nd day Post myocardial infarction syndrome 25th day
L W	67	M	140	265	87	79	77	65	55	Moderate emphysema Uncomplicated course
I P	37	M	110	275	82	75	70	48	53	Recurrent short episodes of supra ventricular tachycardia
R H	61	M	293	370	109	93	85	57	51	Occas PVC ventricular fibrillation 13th day resuscitated
M E	63	F	57	370	111	105	103	73	66	Sinus tachycardia CHF pericardial friction rub 7th day Multiple recurrent episodes ventricular tachycardia 18th to 32nd day
R S	47	M	98	374	116	99	90	74	67	Frequent PVC mild CHF

*T C = total cholesterol †F C = free cholesterol
‡Abbreviations PVC = premature ventricular contraction PAC = premature atrial contraction A V = atrioventricular CHF = congestive heart failure

characterized the changes in free cholesterol over the various incubation times with the latter expressed logarithmically was compared to a slope characterizing the changes in free cholesterol for all of the other subjects (> 300 mg per 100 ml) (Fig 1) This comparison suggested a rather marked increase in esterification in this group with total cholesterol concentrations > 300 mg per 100 ml despite the fact that both diseased and normal subjects were included It was thus postulated that the groups with chronic coronary artery disease and acute myocardial infarction and to a lesser extent, the age matched healthy controls might have had mean esterifications which were overly weighted by the presence of these several subjects whose cholesterol concentrations were > 300 mg per 100 ml

For this reason and because it was felt that a meaningful comparison could be made only if the mean total cholesterol concentration could be held more firmly constant in the four groups, those subjects with total cholesterol concentrations > 300 mg per 100 ml and those with total cholesterol concentrations < 195 mg per 100 ml were removed from the following analysis Note that this resulted in the mean total cholesterol concentrations being held relatively constant (Table VI), the mean level in the young healthy controls being slightly below, and the mean level in the older age

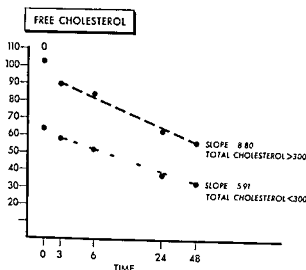


Fig. 1. Comparison of the slopes describing the decrease in free cholesterol after incubation of serum for 3, 6, 24 and 48 hours at 37° C. of nine subjects with total serum cholesterol > 300 mg. per 100 ml. and 37 subjects with total serum cholesterol < 300 mg. per 100 ml. The abscissa (*time*) is expressed logarithmically. 0 refers to mean preincubation control values.

revealed significantly decreased esterification at the $p < 0.01$ level of significance when compared to those age matched healthy controls. Note also the similarity in the slopes of the young healthy and age matched healthy subjects.

Discussion

Our findings indicate that *in vitro* esterification of plasma cholesterol does not change with age in the healthy adult and that it is diminished in patients with coronary artery disease compared to healthy subjects. This latter finding confirms and extends that of Berlin, Oldfelt and Vikrot.[15] However these studies do not pinpoint the mechanism responsible for this difference nor do they indicate that this *in vitro* finding has a physiologic counterpart *in vivo*. This is so because of the substrates necessary for cholesterol esterification only the cholesterol concentration was controlled, and the possible presence of inhibitors and activators of the enzymatic reaction could not be detected, in addition to the fact that the technic itself might not represent a physiologic reaction.

The importance of controlling the level of blood cholesterol is evident from our studies that show that *in vitro* esterification of plasma cholesterol is related to the amount of cholesterol in the blood. This has been found by some[11, 12] and denied by others.[16, 17] Part of the confusion in the literature may be due to the use of different species, differences in measuring esterification, and the failure to separate healthy subjects from those with coronary artery disease. On the other hand, we did not measure the quantity of lecithin in the blood or perform quantitative measurements of lipoproteins of the subjects in the study. We could detect no significant differences in lipoprotein patterns as determined by paper[18] and by cellulose acetate[19] electrophoresis in all of the age matched cholesterol matched subjects nor could we find quantitative differences using densitometric methods of comparison. However, this latter method is regarded by our statistical department as meaningless because of the variable overlapping of the curves representing individual lipoproteins. None of these methods is an adequate substitute for quantitation of all substrates that are essential for esterification and determining the rate of cholesterol esterification. Thus, Nichols and Gong[9] and Ho and Nichols[21] using sonicated dispersions of mixtures of cholesterol and lecithin as substrates for the assay of

Table VA Decrease in free cholesterol (cholesterol esterification) after incubation of serum for 3 6 24 and 48 hours at 37° C

Variables	Young controls	Age matched controls	Acute infarction	Chronic CAD
Number	20	12	12	16
Mean age (range)	27 2 (23–35)	54 6 (36–65)	57 3 (35–73)	56 1 (3[illegible] [illegible]0)
Total cholesterol†	214 2 ± 31 77*	249 6 ± 42 74	264 6 ± 68 4	25? 8 ± 48 2
Free cholesterol†	59 9 ± 11 78	69 2 ± 14 0	81 9 ± 19 9	[illegible]4 8 ± 15 5
Cholesterol esterification†				
3 hours	7 8 ± 3 7	9 5 ± 3 6	9 1 ± 4 9	8 3 ± 3 91
6 hours	13 5 ± 7 9	18 3 ± 8 3	12 8 ± 8 6	12 1 ± 5 0
24 hours	28 2 ± 8 5	33 7 ± 8 0	28 7 ± 13 2	25 1 ± 9 3
48 hours	33 2 ± 7 3	[illegible]9 5 ± 9 5	33 3 ± 13 3	31 3 ± 8 8

*Values given are mean ± standard deviation
†Cholesterol concentrations expressed in mg per 100 ml

Table VB Outcome of comparison of parameters of four groups

Variables	Young controls vs			Age matched controls vs		Acute vs Chronic
	Age matched	Acute	Chronic	Acute	Chronic	
Total cholesterol	p < 0 05	p < 0 01	p < 0 05	N S*	N S	N S
Free cholesterol	N S	p < 0 001	p < 0 02	p < 0 05	N S	N S
Cholesterol esterification						
3 hours	N S	N S	N S	N S	N S	N S
6 hours	N S	N S	N S	N S	p < 0 05	N S
24 hours	N S	N S	N S	N S	p < 0 05	N S
48 hours	N S	N S	N S	N S	p < 0 05	N S

*Values not statistically significant

Table VI Decrease in free cholesterol (cholesterol esterification) after incubation of serum for 3, 6, 24, and 48 hours at 37° C

Variables	Young controls*	Age matched controls	Acute infarction	Chronic CAD
Number	15	10	9	12
Mean age (range)	27 3 (23–32)	56 3 (49–65)	57 4 (35–73)	56 8 (37–[illegible]0)
Total cholesterol†	227 6 ± 23 9	2[illegible]6 5 ± 32 9	229 0 ± 27 0	229 0 ± 25 9
Free cholesterol	63 4 ± 10 53	65 5 ± 12 0	71 9 ± 9 4#	67 8 ± 8 9
Cholesterol esterification†				
3 hours	8 2 ± 3 8	9 0 ± 3 9	7 8 ± 4 0	6 6 ± 2 7
6 hours	14 1 ± 8 8	16 7 ± 6 5	10 7 ± 7 4§	10 0 ± 3 [illegible]‖
24 hours	28 7 ± 9 4	32 1 ± 7 0	25 6 ± 8 9	21 2 ± 7 3¶
48 hours	34 5 ± 7 4	38 9 ± 9 6	27 4 ± 9 0¶	27 2 ± 5 6¶

*Mean total cholesterol concentration held relatively on ta t for all gro [illegible]
† All cholesterol concentrations expressed in mg per 100 ml
‡Values given are means ± standard de iation
§Significantly different from age matcl ed normals at p < 0 05
‖Significantly different from tl e age matched normals at p < 0 02
¶Significantly different from tl e age matched normals at p < 0 01
#Significantly different from tl e young normals at p < 0 05

For all these reasons our *in vitro* findings cannot as yet be interpreted as indicating that patients with coronary artery disease have a decrease in LCAT activity We have however recently demonstrated by incubation of inverted human iliac arterial segments with intima exposed to human serum in which the cholesterol esterifying activity was present and in human serum in which the enzyme has been inactivated by heating to 56 C for 30 minutes that the enzyme must be present for free cholesterol to leave the arterial wall and enter the serum[29] We therefore believe it is important that efforts be made to purify LCAT and to develop methods for measuring accurately its initial rate of activity

Summary

The mean serum *in vitro* cholesterol esterification as determined by the decrease in the concentration of free cholesterol after incubation of serum for 3 6 24 and 48 hours has been compared in four groups subjects with acute myocardial infarction subjects with chronic coronary artery disease age matched healthy controls and young healthy controls

The original data revealed a significantly decreased esterification in subjects with chronic coronary artery disease compared to the group of age matched controls (p < 0 05) and a significantly increased free cholesterol in subjects with acute myocardial infarction compared to the age matched healthy subjects (p < 0 05)

Comparisons of these four groups were then made by removal of those subjects with total cholesterol > 300 mg per 100 ml and < 195 mg per 100 ml because it was felt that a meaningful comparison could be made only if the mean total cholesterol concentration could be held constant for each group This was also done to avoid the possibility that since cholesterol esterification tends to be higher in subjects with hypercholesterolemia those groups with coronary artery disease might show mean esterifications that were overly weighted by the presence of more subjects with total cholesterol > 300 mg per 100 ml When the statistical analysis was performed the mean *in vitro* cholesterol esterification was significantly decreased at 6 hours (p < 0 07) 24 hours and 48 hours (p < 0 01 in) subjects with chronic coronary artery disease compared to age matched controls and was significantly decreased at 6 hours (p < 0 05) and 48 hours (p < 0 01) in subjects with acute myocardial infarction compared to the age matched controls The average slope describing cholesterol esterification over time was significantly decreased in acute myocardial infarction and chronic coronary artery disease (p < 0 01) On the other hand there were no significant differences between the young healthy group and the older age matched healthy subjects

Although these findings suggest the possibility that subjects with coronary artery disease have a deficiency of lecithin cholesterol acyltransferase the limitations of this study are stressed It is unlikely that a firm conclusion will be available until an accurate method of determining the initial rate of plasma cholesterol esterification is available and until the enzyme is purified

We thank Fay Baldwin and Peggy Nickel for their technical assistance and Elizabeth Wolf for her aid in preparation of the manuscript.

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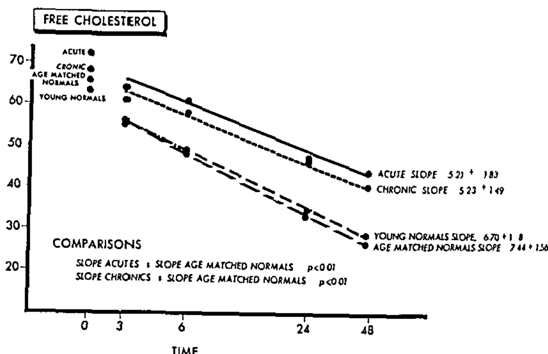


Fig. 2. Comparison of the slopes describing the decrease in free cholesterol after incubation of serum for 3, 6, 24, and 48 hours at 37° C in subjects with chronic coronary artery disease, acute myocardial infarction, age matched controls, and a younger control group; mean cholesterol concentration held constant for all groups. The abscissa (*time*) is expressed logarithmically; 0 refers to mean preincubation control value.

cholesterol esterification found that the rate of enzyme activity might be partly inhibited with increased concentrations of lecithin or with increasing molar proportions of free cholesterol. They postulated that differences in reactivity of the different classes of serum lipoproteins with LCAT may result from differences in the relative proportions of unesterified cholesterol and lecithin on the lipoprotein surface accessible to the enzyme.

Furthermore, because the enzyme responsible for esterification has not been purified, the possibility of the presence of *inhibitors and activators of the enzyme* rather than a decrease in the LCAT enzyme cannot be excluded as one mechanism responsible for differences in cholesterol esterification. Gherondache[2] has demonstrated inhibition of cholesterol esterification during and after infusion of catecholamines. Endogenous catecholamines or elevation of serum free fatty acids which are known to occur with acute myocardial infarction might be one mechanism that explains our initial free cholesterol findings in the group with acute myocardial infarction.

Finally, our *in vitro* findings may have no physiologic counterpart *in vivo*. *In vivo* effects of physical forces, total blood content including its cells,[8] arterial wall[23,25] and particularly the arterial wall LCAT activity,[26,27] were all omitted from our *in vitro* studies. Perhaps most important is our observation that differences in the esterification between the groups at the initial, 3 hour incubation just fell short of statistical significance. This could be due to the small numbers of subjects and to the large individual variations.

It is generally agreed that it is most important to obtain as accurate data as possible on the initial rate of esterification. It is for this reason that another method of measuring cholesterol esterification has been introduced. This method consists of incubating small amounts of plasma for one to six hours at 37° C with a substrate composed of heat inactivated plasma and radioactively labeled free cholesterol added as an albumin stabilized emulsion or coated onto Celite particles with measurement of the formation of labeled cholesterol esters. However, this method has the disadvantage of using exogenous substrates that can produce spurious results. Since our study was completed, Stokke and Norum[8] have developed and reported a method that may circumvent this objection.

Effect of glucagon on automaticity, threshold for stimulation, and atrioventricular conduction in patients with impaired impulse formation or conduction

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John F Williams Jr M D
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The positive inotropic and chronotropic effects of glucagon have been amply demonstrated in both experimental animals[1-4] and man[6-9] The former action encouraged the drug s clinical use and a significant number of patients with heart failure have now received this agent therapeutically Although glucagon s effectiveness appears to vary markedly[10-12] it has been a uniform observation that the hormone is remarkably free of major side effects most noticeable has been the lack of arrhythmias However in the experimental animal glucagon has been found to exert significant electrophysiologic effects The hormone has been reported to enhance atrioventricular (A V) conduction[13] and to reverse the depression of A V conduction produced by propranolol[14] In addition glucagon accelerates nodal pacemakers[15] whereas ventricular automaticity may be unaffected[13,14] or increased[16,17]

At present no systematic investigation of the electrophysiologic effects of glucagon in patients with disorders of impulse formation or conduction has been reported and it is unclear as to whether this agent may produce effects similar to those described in animals In view of the clinical importance of such information the following study was undertaken

Methods

The effect of glucagon on A V conduction was determined in 11 patients with atrial fibrillation or first or second-degree heart block In the four patients with atrial fibrillation in each of whom the ventricular response had been adequately controlled pharmacologically changes in the ventricular rate were used to reflect changes in A V conduction Of the three patients with second-degree heart block two had a fixed 2 1 ventricular response with normal QRS complexes whereas the other had a Mobitz type II block with a varying ventricular response The relationship of atrial to ventricular depolarization was used to measure A V conduction in the patients with heart block

The effect of glucagon on automaticity was assessed in nine patients with ectopic

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Table I Clinical data

P ient	Age	Diagnosis	Rhythm	Heart failure
V J	43	CAHD HCVD	AF	+
L H	40	RHD	AF	+
L B	86	HDUE	AF	+
E T	57	Post aortic valve replacement	AF	+
M B	49	Myotonia dystrophica	1 HB	−
A. C.	50	HCVD	1 HB	+
J L	61	HDUE	1 HB	−
C P	/3	COPD	1 HB	+
W E	70	HDUE	2 HB	−
W P	74	HDUE	2 HB	−
E C	64	HDUE	? HB	−
M R.	27	Congenital heart block	3 HB†	−
R. Mc.	29	Congenital heart block	3 HB†	−
R C	60	CAHD	3 HB†	+
M G	/9	CAHD	3 HB†	+
E K	73	CAHD	3 HB	−
G T	68	CAHD	3 HB	−
M O	/5	CAHD	3 HB	−
C F	5	CAHD—digitalis intoxication	Nodal tachy cardia	− −
V S.	37	Amyloidosis	Sinus arrest nodal rhythm	−

CAHD C ronary atherosclerotic h rt d se se
HCVD Hypert e cardio scula d se se
RHD Rhe m tic heart d sease.
HDUE Heart disease of ud t rm ned tiol gy
COPD Chronic bstructi e p lm ty d se se
HB Heart block († normal QRS d atio)
AF A ial fibrillation.
† Present.

pacemaker in the three patients with complete heart block and wide QRS complexes Whether these latter patients had pacemakers distal to the bifurcation of the b ndles or bundle branch block with the pacemaker proximal to the bifurcation was not determined However the latter mechanism is suggested in patient M O whose control rate was generally faster than that expected with an idioventricular pacemaker In the patient with sinus arrest and a nodal escape mechanism a slight increase in the rate of this pacemaker was observed after glucagon Since the cardiac effects of injections of glucagon generally appear and dissipate fairly rapidly[4,5] the increase in rate which occurred relatively late and persisted throughout the remainder of the study in this patient may represent spontaneous variation and not glucagon effect In the patient with digitalis induced nodal tachycardia a maximum increase of only 6 beats per minute was observed

Six of the 20 patients had ventricular premature contractions during the control period No significant change in the frequency of the premature contractions was noted during the study

The effect of glucagon on the threshold for ventricular stimulation is presented in Table IV In all patients stimulation threshold had been reproducible on multiple determinations before glucagon In only one of the nine patients was a significant change in stimulation threshold observed after glucagon In this patient threshold increased by 60 per cent at the 3 minute period but returned to control by 10 minutes

No significant change in systemic arterial pressure was observed after glucagon The only side effects noted with glucagon were

pacemakers by determining the drug's effect on the rate of this pacemaker. Seven patients had complete heart block, four with QRS complexes of normal duration. Two patients had nodal pacemakers with apparently normal A-V conduction. One of these latter patients had a digitalis-induced nodal tachycardia, whereas the other had persistent sinoatrial asystole but could be paced from the atrium up to a rate of 140 per minute with no evidence of impaired A-V conduction. In patients with intracardiac pacemakers the spontaneous rate was determined during cessation of pacing and only those patients who could tolerate this without developing symptoms were selected for study.

The effect of glucagon on threshold for stimulation was determined in nine patients with temporary transvenous pacemakers. A Cordis Synchrocor II which permits stepwise changes in current flow of 0.1 ma. was used as the external power source. The minimal milliamperage necessary for stimulation was determined on several occasions and thereafter was maintained at the lowest setting which permitted constant pacing; pacing rate ranged from 70 to 80 beats per minute. After glucagon administration the minimal milliamperage necessary for stimulation was again determined at each of the periods designated below. The stimulation threshold was determined from the settings on the power supply and therefore was not necessarily that delivered to the endocardium.

Six patients were receiving a digitalis glycoside but in only one was this substantiated as being a causative or contributing factor to the arrhythmia. No patient had suffered a myocardial infarction within the preceding six weeks and with the exception of the patient with nodal tachycardia the existing cardiac rhythm had been stable for at least seven days preceding the study.

Indirect or direct brachial arterial pressure and standard Lead II of the electrocardiogram (ECG) were recorded in all patients. Furthermore, in two patients with first degree heart block atrial, ventricular, and His bundle potentials were recorded with intracardiac electrodes utilizing the technique described by Damato and associates.[18]

In all patients an infusion of 5 per cent glucose in water was begun and after control measurements were obtained 5 mg. of glucagon dissolved in normal saline was given intravenously over 30 seconds. Measurements of blood pressure, 30 second recordings of the standard ECG, and when appropriate, stimulation threshold were obtained 1, 3, 5, 10, 15, and 30 minutes after completion of the injection. In the patients with first degree heart block brief recordings at a paper speed of 100 mm. per second were also obtained at these time periods.

Results

The clinical data for each individual are given in Table I.

The individual results of the effect of glucagon on A-V conduction are presented in Table II. No clinically significant change in ventricular rate occurred in patients with atrial fibrillation following glucagon injection. One of these patients (E. T.) required propranolol (80 mg. per day) as well as digoxin to control his ventricular response before glucagon. In the four patients with first degree heart block the P-R interval increased by only 10 msec. in one, was unchanged in another, and decreased by a maximum of 15 msec. in the remaining two. In the latter two patients recordings from intracardiac electrodes revealed that the decrease in P-R interval, which was maximum at the 1 minute period and thereafter returned toward control, resulted from a decrease in the P-His bundle interval with an unchanged H-Q interval. In none of the patients with second degree block was there a significant change in conduction following glucagon administration. Although not included in Table II, glucagon did not restore A-V conduction in any patient with complete heart block.

The effect of glucagon on automaticity is presented in Table III. In three of the four patients with complete heart block and pacemakers above the bifurcation of the bundles no change in the rate of the dominant pacemaker was observed after glucagon. In the remaining patient the rate increased by a maximum of 10 beats per minute at the 1 minute period and thereafter returned toward control values. Glucagon did not alter the rate of the dominant

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Patient	*Age*	*Diagnosis*	*Rhythm*	*Heart failure*
V J	43	CAHD HCVD*	AF	+
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E. R.	73	CAHD	3 HB	−
G T	68	CAHD	3 HB	−
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C. F	75	CAHD—digitalis intoxication	Nodal tachycardia	−
V S	37	Amyloidosis	Sinus arrest nodal rhythm	−

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Table III *Effect of glucagon on automaticity*

Patient	Ventricular rate (beats/min)						
	Control	Minutes after injection					
		1	3	5	10	15	30
3° heart block normal QRS							
M. R.	44	—	44	46	44	44	—
R. Mc.	45	48	45	45	45	42	43
R. C.	60	60	66	64	60	60	—
M. G.	59	56	60	54	54	56	57
Wide QRS							
E. R.	37	37	37	37	37	37	35
G. T.	35	38	38	38	35	34	34
M. O.	72	72	72	72	72	72	—
Nodal tachycardia							
C. F.	136	136	136	136	142	140	136
Sinus arrest nodal pacemaker							
V. S.	44	44	44	48	48	50	50

Table IV *Effect of glucagon on stimulation threshold*

Patient	Control (ma)	Minutes after injection					
		1 (ma)	3 (ma)	5 (ma)	10 (ma)	15 (ma)	30 (ma)
A. C.	1.3	1.3	2.1	1.9	1.3	1.3	1.3
W. E.	0.8	0.8	0.8	0.8	0.8	0.8	0.8
E. C.	1.0	1.2	1.0	1.2	1.3	1.1	1.1
V. S.	10.0	10.5	10.5	10.0	10.0	10.0	10.1
M. G.	8.0	8.0	8.0	7.0	7.0	8.0	8.0
R. C.	0.8	0.8	0.8	0.8	0.8	0.8	0.8
E. R.	0.9	0.8	0.9	0.9	1.0	1.0	1.0
R. M.	2.3	2.4	2.4	2.4	2.3	2.2	2.3
M. O.	0.8	0.8	0.8	0.9	0.8	0.8	—

In a single study in man glucagon was reported to decrease first-degree heart block and to restore sinus rhythm in patients with complete heart block or supraventricular tachycardia.[19] However these patients had cardiogenic shock or acute left ventricular failure at the time of the study and the authors attributed the electrophysiologic improvement to the positive inotropic effects of the hormone.

The lack of effect of glucagon on nodal and ventricular pacemakers in man also is in contrast to its effect on nodal[13,15] and ventricular automaticity[16,17] in dogs. Enhancement of the latter, however, has not been a universal observation.[13] Others have reported that glucagon at the same dose per unit of body weight produced a greater chronotropic and inotropic effect in dogs than in man,[20] suggesting that species differences may produce or contribute to these disparate results concerning the drug's electrophysiologic effects.

We are unaware of any report concerning

Table II. Effects of glucagon on atrioventricular conduction

Patient		Control	Minutes after injection					
			1	3	5	10	15	30
Atrial fibrillation								
V J	Ventricular rate beats per minute	75-80	80	80	76	84	84	76
L H	Ventricular rate beats per minute	70-74	74	70	76	76	66	68
L B	Ventricular rate beats per minute	75-80	80	80	76	84	84	76
L I	Ventricular rate beats per minute	80-84	84	88	84	80	84	86
1° heart block								
M B	Atrial rate	76	76	76	74	74	74	74
	P-R interval (msec.)	250	260	260	250	250	250	250
V C	Atrial rate	74	76	74	74	74	74	74
	P-R interval (msec.)	230	230	230	230	230	230	—
J L	Atrial rate	85	88	94	78	78	80	—
	P-R interval (msec.)	210	195	210	200	210	210	—
	P-H (msec.)	165	150	155	155	165	165	—
	H-Q	45	45	45	45	45	45	—
C P	Atrial rate	90	93	95	90	90	—	—
	P-R interval (msec.)	210	195	210	220	220	—	—
	P-H	160	145	160	170	170	—	—
	H-Q	50	50	50	50	50	—	—
2° heart block								
W L	Atrial rate	68	78	80	78	78	74	[illegible]
	Ventricular rate	34	39	40	39	39	37	36
W P	Atrial rate	65	68	71	68	68	64	64
	Ventricular rate	37	36	36	36	36	35	37
E C	Atrial rate	88	100	96	96	94	88	86
	Ventricular rate	44	50	48	48	47	44	43

nausea and vomiting which occurred in two patients.

Discussion

With few exceptions glucagon produced no significant change in A-V conduction, nodal or ventricular automaticity, or threshold for stimulation in this study.

The lack of effect of glucagon on A-V conduction in these patients is in contrast to that observed in animals where glucagon enhanced conduction or restored 1:1 conduction in animals in which 2:1 block had been produced.[13] In this latter study it was observed that glucagon decreased the P-His bundle interval without affecting the H-Q interval. In two patients in the present study in whom His bundle electrograms were obtained, the pre-existing block occurred proximal to the His bundle deflection. In both glucagon shortened the P-H interval without affecting the H-Q interval. The maximum shortening, however, was only 15 msec. and was brief in duration.

Whitsitt and Lucchesi[14] also reported that glucagon reversed the depression of A-V conduction produced by propranolol in dogs. In our study no increase in ventricular rate was observed after glucagon in the one patient with atrial fibrillation receiving propranolol in addition to digoxin to control his ventricular rate.

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the effect of glucagon on the threshold for ventricular stimulation In eight of the nine patients of this study no change in threshold was observed after glucagon Thus the administration of glucagon to patients requiring ventricular pacemakers is unlikely to cause pacing failure However, since a 60 per cent increase in stimulation did occur in one patient, careful observation should be given if glucagon is employed under these conditions

It has been observed that the positive inotropic effect of glucagon is reduced or absent in the presence of chronic congestive heart failure[10, 11] Although hospitalization was precipitated by the development of heart failure in several of our patients all were clinically well compensated at the time of the study Furthermore, the majority of patients had not developed this complication Thus the failure to observe significant electrophysiologic changes after glucagon cannot be attributed to the presence of chronic congestive failure

To avoid the depressant action of phenol which is contained in the commercially available diluent glucagon was dissolved in normal saline immediately before administration to each patient The increase in sinus rate which occurred in most patients with sinus rhythm indicates that the glucagon administered was pharmacologically active Furthermore glucagon from the same lot was dissolved in saline and added to the bath of isometrically contracting cat papillary muscles (final concentrations 20 μg per milliliter), a near doubling of the force of contraction was observed

The dose of glucagon selected for this study is similar to that employed in previous studies of the cardiovascular effects of glucagon in man and approaches the maximal amount that can be given by rapid injection without an inordinate degree of nausea or vomiting Whether different results would be obtained with larger amounts or continuous infusions of this agent is unclear Similarly patients with disorders of impulse formation or conduction caused by conditions other than those afflicting our patients may respond in a different manner It must also be appreciated that glucagon can lower serum potassium concentrations,[6, 9] an undesirable occurrence in patients receiving digitalis glycosides

Nevertheless, the present results, combined with the lack of significant arrhythmias observed in any of the previous studies of glucagon in man, indicate that the direct electrophysiologic effects of this hormone are unlikely to be clinically important

Summary

Glucagon (5 mg) was injected intravenously into patients with stable disorders of impulse formation or conduction during electrocardiographic monitoring The ventricular rate did not change significantly in any of the four patients with atrial fibrillation nor did glucagon alter A V conduction in any of the three patients with second degree heart block In two patients with first degree heart block the P R interval shortened briefly by a maximum of 15 msec, the shortening due entirely to a decrease in the P His bundle interval with no change in the H Q interval In two additional patients with first degree block the P R interval remained essentially unchanged In seven patients with complete heart block, four with QRS complexes of normal duration, glucagon did not affect the rate of the spontaneous pacemaker Similarly in two patients with nodal pacemakers and normal A V conduction, glucagon was without significant effect In only one of nine patients with a functioning temporary transvenous pacemaker was a significant change in the threshold for stimulation observed

These results indicate that glucagon is unlikely to produce electrophysiologic effects of clinical importance in patients with impaired impulse formation or conduction

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leads during the control period and at the end of each 30 minute interval simultaneous with the above blood samples Time marks were also recorded (10 and 100 msec) using a model 184 Tektronix time mark generator These records were analyzed for changes in duration and/or configuration of P PR QRS QT ST segment and T wave

Results

There was a relatively wide range in blood levels of lidocaine (Fig 1) at any given infusion concentration despite identical infusion techniques in all patients Although no patient was known to have intrinsic liver disease several of the patients were in a state of minimal congestive heart failure Nevertheless the highest levels were obtained in the patient without any evidence of cardiac or hepatic decompensation (8 2 mg per liter Patient S B see Fig 2) There was however a relatively linear relationship between the infusion concentration and mean serum lidocaine level (Fig 1) Two patients showed clinical signs of toxicity manifest as lethargy but did not demonstrate a decrease in arterial blood pressure even at toxic blood levels Despite the variation in heart rate for any individual over the 2½ hour study period no definite trend emerged with relation to serum lidocaine levels (Table I)

Similarly the PR interval QRS duration and QT interval showed no consistent change which would correlate with the patients determined serum lidocaine level (Table I)

Even in those patients subsequently found to have serum lidocaine levels generally accepted to be in the toxic range no change was found in any of the above parameters In addition the QRS and T vectors also showed no change in correlation with the serum lidocaine level Fig 2 shows an example in one of our patients of the series of orthogonal lead recordings made during one of experimental infusion studies.

Discussion

Clinical properties Lidocaine a local anesthetic has been found to possess significant antiarrhythmic effects It was ini-

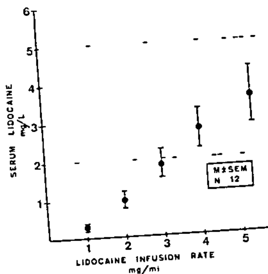


Fig 1 Serial measurements of serum lidocaine levels The lidocaine infusion rates are plotted on the horizontal axis and the corresponding serum lidocaine levels at the end of a ½ hour infusion period are plotted on the vertical axis

tially anticipated that these properties would be similar if not identical with procaine amide which is another local anesthetic of very similar structure However early clinical investigation showed considerable deviations in these two agents antiarrhythmic spectrum Procaine amide was found to be effective against premature atrial junctional and ventricular beats as well as various supraventricular arrhythmias [16] Lidocaine in contrast was found to be ineffective against atrial arrhythmias [17 18] Furthermore procaine amide in both therapeutic and toxic levels was shown to prolong A V conduction intraventricular conduction and ventricular repolarization [18 19 20] However a recent clinical study by Rosen and associates[14] showed lidocaine to have minimal if any change in A V or ventricular conduction when a single or repeat bolus of lidocaine in generally accepted therapeutic doses (1 to 2 mg per kilogram) was given intravenously [14] This dosage regimen may be expected to produce blood levels of 1 to 10 mg per liter for at least 30 minutes in the absence of significant congestive heart failure or liver disease [21]

Electrophysiologic properties Lidocaine and procaine amide have likewise been contrasted in their effects on action potential

Effect of lidocaine on the scalar orthogonal electrocardiogram

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Lidocaine was first used for the treatment of cardiac arrhythmias in 1959.[1] Since that time it has been used increasingly for the treatment of ventricular ectopic beats associated with acute myocardial infarction and arrhythmias secondary to digitalis toxicity.[2-4] The drug's relatively minor negative inotropic effect when compared to procaine amide or quinidine makes it particularly desirable as an antiarrhythmic agent in acute myocardial infarction.[5-7]

Extensive electrophysiologic studies are available on the effects of lidocaine and the relationship to its clinical antiarrhythmic properties.[8-14] Characteristic findings noted in concentrations considered therapeutic have been shortening of action potential duration and effective refractory period as well as a possible increase in intraventricular conduction velocity. It has therefore been suggested that in the clinical setting lidocaine may shorten both intraventricular conduction and the Q-T interval of the standard electrocardiogram (ECG). Based on such experimental data it was elected to study the clinical effects of graded doses of intravenous lidocaine on the body surface ECG.

Methods

Twelve patients (five female, seven male, age range 44 to 75) were selected for study on the basis of the following criteria: sinus rhythm, normal A-V and intraventricular conduction and refraining from drugs with known effects on the ECG for at least 72 hours prior to study. All patients had a history of recurrent ventricular premature beats.

After obtaining informed consent, lidocaine HCl was infused at a constant rate by Harvard infusion pump at successive rates of 1, 2, 3, 4, and 5 mg. per minute for half hour intervals, respectively. Serum lidocaine levels*[15] were determined at each half hour interval just prior to increasing the infusion rate. Body surface ECG's were obtained at a 200 mm. paper speed (Hewlett Packard No. 1508 A three-channel ECG amplifier Honeywell No. 1508 visicorder) by use of a simultaneous display of the scalar X, Y, and Z Frank orthogonal

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leads during the control period and at the end of each 30 minute interval simultaneous with the above blood samples Time marks were also recorded (10 and 100 msec) using a model 184 Tektronix time mark generator These records were analyzed for *changes in duration* and/or configuration of P PR QRS QT ST segment and T wave

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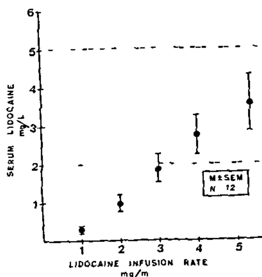


Fig 1 Serial measurements of serum lidocaine level The lidocaine infusion rates are plotted on the horizontal axis and the corresponding serum lidocaine levels at the end of a ½ hour infusion period are plotted on the vertical axis

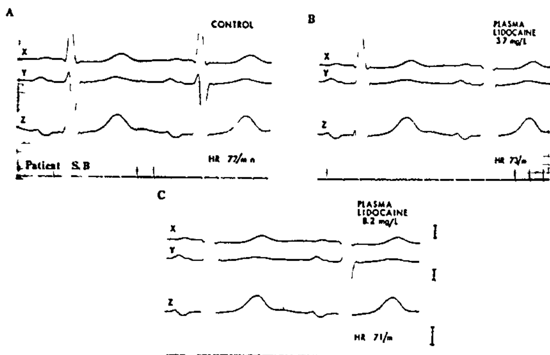


Fig 2 The effect of lidocaine on the ECG Scalar Frank orthogonal leads (X, Y, and Z) are displayed in each panel Time lines are recorded at the bottom of each panel and recur every 10 msec and 100 msec. Voltage (0 5 mv) calibrations for each lead are shown to the right of panel *C* Note the slight decrease in sinus rate without significant change in any other variable

characteristics of isolated Purkinje fiber–ventricular muscle preparations [8, 11, 2] Procaine amide has been shown to increase slightly the action potential duration (APD) of both Purkinje and ventricular muscle fibers and increase the effective refractory period (ERP) of these tissues [2] Lidocaine, in contrast (in concentrations thought to represent therapeutic blood levels), has been shown to decrease the APD as well as ERP of both Purkinje and ventricular muscle fibers [8, 9, 11] Both these drugs however have been shown to have a $\Delta APD/\Delta ERP$ of <1 [8, 9, 11, 16] Nevertheless previous studies[8, 9] refer to lidocaine's shortening of the APD as a possible important mechanism in this drug's antiarrhythmic action Since decremental conduction has been suggested to be an important factor in re-entry mechanism lidocaine's effect on the APD would, in part serve to abolish arrhythmias sustained by re-entry [2] The decrease in the APD previously described consists of a shortened phase 2 with an increased slope of phase 2 and phase 3 of the Purkinje fiber and ventricular muscle action potential [8, 9, 11] It is generally accepted that the S-T segment of the ECG in the intact heart corresponds to phase 2 of the action potential [4] If APD did, in fact, shorten with therapeutic levels of lidocaine, then in our study the S-T segment should have shortened, at least at our highest lidocaine blood levels The present results suggest that this effect may not be a significant mechanism of lidocaine's antiarrhythmic action in man when given in therapeutic doses It is however possible that the more pronounced effects seen in vitro in Purkinje fiber as compared to ventricular muscle may, in fact be responsible for the lack of significant repolarization changes following lidocaine

In our study with the Frank scalar orthogonal display we used the longest measurement from these leads to preclude any change in vector from affecting the measurement It therefore appears from our data that the therapeutic dose range in man may more closely approximate a lower lidocaine level than that assumed by the previous in vitro studies [8, 9, 11] Lidocaine at between 5×10^{-6} and 1×10^{-7} M per liter, described by these investigators, produced no change in the APD or membrane responsiveness An increase in membrane

Table I. Lidocaine infusion rate (mg/min)

Parameter	Control	1 mg/min	2 mg/min	3 mg/min	4 mg/min	5 mg/min
P-P (msec.)	794 ± 77	835 ± 107	815 ± 73	804 ± 67	806 ± 110	796 ± 132
P-R (msec.)	174 ± 15	172 ± 21	171 ± 18	171 ± 17	172 ± 22	170 ± 19
QRS (msec.)	97 ± 9	101 ± 10	100 ± 10	101 ± 9	99 ± 12	97 ± 10
Q-T (msec.)	442 ± 58	433 ± 49	436 ± 67	423 ± 59	427 ± 55	410 ± 60
BP (mm. Hg)						
Systolic	133 ± 9	134 ± 8	136 ± 11	140 ± 10	139 ± 10	138 ± 12
Diastolic	88 ± 3	88 ± 3	93 ± 3	92 ± 3	92 ± 4	90 ± 6

M ± S.E.M. N = 12
No values following lidocaine infusion were found to differ statistically from control (t test for paired samples)

responsiveness at 1×10^{-5} would increase conduction and thus prevent decremental conduction and the resultant re-entry. Again, if our proposed therapeutic in vivo concentrations are used, this effect on membrane responsiveness would therefore not be present. However, the shortening effect of lidocaine on refractoriness, especially the relative refractory period, was present in vitro even at the lower concentrations. This effect would possibly serve to decrease the chance for local decremental conduction and therefore diminish the incidence of ectopic beats. Finally, our proposed therapeutic in vitro concentration would still decrease the automaticity of phase 4 depolarization in Purkinje fibers according to previous data.[8]

Blood levels. Since lidocaine has no deleterious effect on the ECG and only slight negative inotropic effects in the low toxic range,[1] the chief clinical guide to toxic blood levels has been the central nervous system effects including drowsiness, incoordination, jitteriness, and frank convulsions. Hepatic metabolism is the major pathway for removal of the drug and Thompson and co-workers[1] have recently emphasized the danger of encountering toxic levels in patients in congestive heart failure with hepatic engorgement. The experience in our patients (Fig. 1) demonstrates the wide range of serum levels after constant infusion of this drug in patients without clinical hepatic disease or congestive heart failure. Stable serum levels even with constant infusion techniques would not be expected however for 8 to 12 hours.[26] It would be anticipated that the standard gravity drip used in most cardiac care units to infuse lidocaine would further tend to increase the variability in blood levels actually achieved in patients. If control of arrhythmias in a given patient requires levels just under those producing central nervous system symptoms, it would seem imperative that a more accurately controlled method of infusion be used.

Summary

In summary, our data indicate that therapeutic serum levels of lidocaine demonstrate no electrocardiographic change, and especially no shortening of the Q-T interval. This suggests that the therapeutic in vitro lidocaine level may be less than previously assumed.

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Effects of ouabain on cardiac output and pulmonary blood flow in dogs

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In 1926 Harrison and Leonard[1] reported that digitalis caused a paradoxical decrease in the cardiac output of dogs with nonfailing hearts despite increased efficiency of systolic contraction More recently several reports[2-4] have confirmed these findings in normal human subjects In other canine studies Dock and Tainter[5] noted that digitalis caused decreased central venous pressure increased systemic arterial and portal venous pressures and an increased hepatosplenic volume They postulated that hepatic vein constriction trapped blood in the abdominal viscera accounting for a decreased venous return Others[6,7] subsequently confirmed these findings Cotten and Stopp[8] using a cannulating rotameter in the aortic arch of dogs with nonfailing hearts reported that ouabain increased contractility peripheral resistance and blood pressure but that it decreased left ventricular output heart rate and arterial pressure When left atrial pressure was maintained by infusion of blood ventricular output and stroke work increased Ross and associates[9] observed similar responses in dogs on cardiopulmonary bypass who were given acetylstrophanthidin

Recently Harrison and co workers[10] have studied the effects of ouabain on the splanchnic circulation of dogs they have noted a significant precapillary constriction but no significant changes in splenic and gut weight or liver blood volume Moreover some recent data on normal human subjects[11,12] have failed to substantiate earlier reports of a decreased cardiac output after digitalization In light of these reports we undertook the present study to quantify cardiocirculatory responses to ouabain in dogs with nonfailing hearts by means of direct flowmetry on the aortic arch and pulmonary artery To further evaluate the possibility that ouabain evokes pulmonary pooling of blood we also studied a constantly perfused isolated lung lobe preparation[13]

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Methods

Eighteen mongrel dogs weighing 16 to 24 kilograms were divided into three equal groups for study of (a) aortic blood flow, (b) pulmonary artery blood flow, and (c) volume changes and pressure in the isolated lung lobe. All dogs were anesthetized with intravenously injected sodium pentobarbital (30 mg. per kilogram). After endotracheal intubation, each animal was placed on a respirator (Harvard Apparatus) with an inspiratory rate set at 14 to 18 cycles per minute and a tidal volume of 250 to 350 ml., depending upon the size of the dog. The right femoral artery was cannulated for measurement of arterial pressure via a strain gauge transducer (Statham). The right femoral vein was cannulated for injection. Lead II of the electrocardiogram was recorded continuously on each dog.

Aortic blood flow group. Each of the 6 dogs in this group was subjected to a midline laparotomy and cannulation of the portal vein. Pressure in the portal vein was recorded with a saline manometer. The incision was closed and the animal was then placed in a right lateral decubitus position for a left thoracotomy at the fourth intercostal space. The pericardium was incised and the proximal aorta was isolated. A 14 or 16 mm. (inner diameter) electromagnetic blood flow transducer (Micron) was positioned around the aorta and connected to a flowmeter amplifier (Micron). The left external jugular vein was cannulated with the catheter tip positioned at the level of the right atrium for monitoring central venous pressure (CVP) via a saline manometer. In this series of dogs we recorded aortic blood flow, i.e., left ventricular output minus coronary blood flow (AQ), mean systemic arterial blood pressure (SAP), portal venous pressure (PVP), and heart rate (HR) on a polygraph (Sanborn). Total peripheral resistance (TPR) was calculated from (SAP-CVP)/AQ. After a 30 minute period of stabilization, each dog was injected intravenously with 5 ml. of the solvent used in the commercial ouabain preparation and was observed for an additional 30 minutes. At the end of this period 5 ml. of ouabain (Lilly), 45 μg per kilogram of body weight, was infused for one minute into the right femoral vein. With the end of ouabain infusion considered as zero time, measurements were recorded at 2.5, 5, 7.5, 10, 12.5, 20, and 30 minutes.

Pulmonary artery group. Six dogs were subjected to a left thoracotomy in the fourth intercostal space. A catheter was inserted into the right atrium via the jugular vein. The pulmonary artery was isolated and an electromagnetic flow probe (Micron) of 12 or 14 mm. (inner diameter) was positioned around the vessel. Pulmonary artery blood flow (PAQ), SAP, CVP, and HR were recorded. After a period of stabilization, each dog received a 5 ml. intravenous injection of ouabain carrier solution and was observed for 30 minutes. Ouabain (45 μg per kilogram) was then administered intravenously in a 5 ml. volume. In both the cardiac output and pulmonary artery groups, blood flow probes were calibrated with canine whole blood.

Isolated lung lobe group. Six dogs were subjected to a thoracotomy at the left fifth interspace. The left lower pulmonary artery and vein were isolated and divided. Tygon tubing (1/4 inch inner diameter) was used to cannulate the divided vessels toward the isolated lobe. An arterial reservoir was elevated so that pulmonary artery pressure to the isolated lung lobe was in the range of 10 to 20 mm. Hg. After flow was established, the ribs were approximated and the incision was closed by suturing. A chest tube was used with an underwater seal and the animals breathed spontaneously. A peristaltic pump (Sigmamotor) transferred blood from the venous to the arterial reservoir. Mean blood flow was held constant during each experiment. Left lower pulmonary artery and systemic arterial pressures were continuously recorded with pressure transducers (Statham) connected to a 4 channel recorder (Grass). After a period of stabilization, 5 ml. of ouabain carrier solution was introduced into the arterial reservoir and readings of net volume change across both reservoirs were taken at 2.5, 5, 10, 15, and 20 minutes. After another 10 minutes of stabilization, 5 ml. of ouabain (50 μg per kilogram) were introduced into the arterial reservoir and readings were obtained as previously mentioned. Changes in pulmonary artery pressure were directly proportional to changes in pulmonary vascular resistance and a decrease in the level

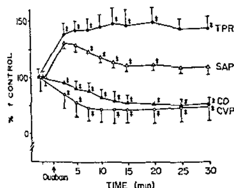


Fig 1 Effects of ouabain on total peripheral resistance (*TPR*) systemic arterial pressure (*SAP*) aortic blood flow (*CO*) and central venous pressure (*CVP*) over a 30 minute period in 6 dogs Values are expressed as percentage change (± S E) from the values at zero time Asterisks indicate a significant (p < 0 05) difference from zero time values

Table I Effects of ouabain on portal pressure and heart rate in cardiac output group

Time (min)	Portal venous pressure (mm saline)	Heart rate* (beats/min)
0	105 ± 9 1	159 ± 6 8
2 5	107 ± 9 1	154 ± 7 7
5 0	110 ± 9 4†	153 ± 7 1
7 5	111 ± 10 0†	146 ± 7 9†
10 0	112 ± 9 7†	149 ± 7 8
12 5	111 ± 9 3†	149 ± 8 1
15 0	110 ± 8 9†	147 ± 7 9†
20 0	108 ± 8 8	147 ± 10 0†
25 0	106 ± 9 2	149 ± 10 8
30 0	107 ± 8 9	149 ± 9 3

*Mean ± S E.
†Significantly different from control (time 0)

of the venous reservoir indicated sequestration of blood in the isolated lung lobe

The mean values within each group were statistically compared by Duncan s New Multiple Range Test.[14] Differences were considered significant at a probability level of less than 0 05

Results

Aortic blood flow Initial control values (including standard error) were SAP 91 ± 3 4 mm Hg CVP 28 ± 3 4 mm of saline AQ 1 914 ± 135 ml per minute TPR 0 047 ± 0 004 mm Hg/ml^{-1}/min^{-1} PVP 106 + 8 6 mm of saline and HR 156 ± 8 0 beats per minute The administration of ouabain carrier solution elicited no significant changes in any of these measurements After 30 minutes the following values were recorded SAP 89 ± 3 3 mm Hg CVP 27 ± 3 1 mm of saline AQ 1 895 ± 141 ml per minute TPR 0 047 ± 0 005 mm Hg/ml^{-1}/min^{-1} PVP 105 ± 9 1 mm of saline and HR 159 ± 6 8 beats per minute

Intravenous injection of ouabain (45 µg per kilogram) produced significant changes at various times in all parameters during the next 30 minutes (Fig 1) At 2 5 minutes SAP increased 30 per cent to 115 mm Hg (p < 0 05) Thereafter SAP gradually declined but was still significantly elevated above control values until 25 minutes after ouabain injection After the administration of ouabain CVP fell 16 per cent to 22 mm of saline (p < 0 05) and continued to decrease at 12 5 minutes after ouabain injection it was 19 mm of saline (p < 0 05) CVP was significantly lower than control values at all times after ouabain was injected Mean AQ fell 6 per cent at 2 5 minutes to 1 778 ml per minute (p < 0 05) and to 1 499 ml per minute (−21 per cent) at 12 5 minutes (p < 0 05) At 25 minutes AQ had fallen 25 per cent to 1 426 ml per minute (p < 0 05) TPR was significantly elevated at all times after administration of ouabain It rose rapidly from 0 047 to 0 066 mm Hg/ml^{-1}/min^{-1} (a 41 per cent increase) at 5 minutes and remained significantly above control values Mean PVP was 105 mm of saline before ouabain was injected increasing thereafter (Table I) PVP was significantly elevated to 110 mm of saline at 5 minutes (p < 0 05) it peaked to 112 mm of saline at 10 minutes (p < 0 05) and then gradually declined Mean HR (Table I) gradually declined after ouabain injection from 159 to 146 beats per minute at 7 5 minutes (p < 0 05) after which it began to rise again reaching 149 beats per minute at 25 minutes

Pulmonary artery group Initial control values were SAP 92 ± 6 1 mm Hg CVP 26 ± 2 6 mm of saline PAQ 2 423 ± 255 ml per minute and HR 160 ± 9 3 beats per minute The administration of ouabain solvent elicited *no significant changes* in any of the parameters After 30 minutes of

*Table II. Comparison of net volume changes across the blood reservoirs in the isolated lower lung lobe after addition of ouabain solvent and ouabain to the arterial reservoir**

Dog No.	0	2.5 min	5.0 min	10.0 min	15.0 min	20.0 min
Solvent						
1	—	0	+1	+1	+1	+1
2	—	−2	−2	−2	−2	−2
3	—	+2	+4	+3	+2	+1
4	—	0	0	−1	−3	−3
5	—	+6	−3	−2	−1	0
6	—	0	−1	0	0	+1
Mean	—	+1.0	+0.8	+0.3	−0.2	−0.3
S.E. ±	—	1.1	1.0	0.8	0.8	0.7
Ouabain						
1	—	+1	+3	+3	+2	−1
2	—	+5	+6	+7	+6	+6
3	—	0	−1	−1	−1	−3
4	—	−1	−2	−4	−3	−4
5	—	+1	−3	0	0	0
6	—	+1	+1	+4	+2	+3
Mean	—	+1.2	+0.7	+1.5	+1.0	+0.2
S.E. ±	—	0.8	1.4	1.6	1.3	1.5

*A negative value indicates trapping of blood in the lung lobe; a positive value indicates sequestration in the reservoirs.

continuous monitoring, the following values were recorded: SAP, 92 ± 5.3 mm. Hg; CVP, 26 ± 2.8 mm. of saline; PAQ, 2,455 ± 259 ml. per minute; and HR, 164 ± 8.7 beats per minute. These served as control values.

The administration of ouabain caused significant changes at various times in all parameters during the next 30 minutes (Fig. 2). SAP was increased 29 per cent to 119 mm. Hg at 2.5 minutes after ouabain injection and then gradually fell to 100 mm. Hg by 30 minutes. SAP was significantly ($p < 0.05$) elevated above control values at all time periods after drug administration. CVP fell 31 per cent to 18 mm. of saline at 2.5 minutes and continued to decline until 10 minutes when it was 16 mm. Subsequently, it gradually began to return toward the control value. CVP was significantly ($p < 0.05$) decreased at all time periods after ouabain injection. PAQ was significantly ($p < 0.05$) less than control at all time periods. Mean PAQ fell 19 per cent to 1,998 ml. per minute at 2.5 minutes and then gradually returned toward the control value. PAQ was 2,150 ml. per minute at 30 minutes (12 per cent below control). Mean HR decreased after injection of ouabain to 151 beats per minute at 12.5 minutes ($p < 0.05$) and was still significantly less than control at 30 minutes (148 beats per minute).

Isolated lung lobe group. Addition of ouabain carrier solution to the arterial reservoir in the isolated lung lobe series caused no significant net volume changes, nor did the addition of ouabain (50 μg per kilogram) to the arterial reservoir (Table II).

However, the ouabain carrier solution decreased pulmonary artery pressure from 194 to 190 mm. of saline at 2.5 minutes. At each subsequent reading up to 20 minutes a significant decrease in pressure was observed (Table III). The addition of ouabain to the arterial reservoir evoked a significant ($p < 0.05$) increase in pulmonary artery pressure at all time periods to 20 minutes (Table III).

Discussion

Rapid digitalization with ouabain decreased aortic blood flow, pulmonary artery blood flow, central venous pressure, and heart rate in anesthetized dogs with nonfailing hearts. Ouabain also increased their

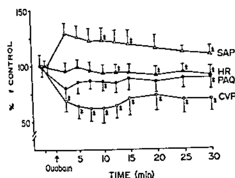


Fig 2 Effects of ouabain on SAP heart rate (HR) pulmonary artery blood flow (PAQ) and CVP in 6 dogs.

systemic arterial and portal venous pressures and total peripheral and pulmonary vascular resistances These findings indicate that cardiac glycosides have two major effects on the normal circulation (a) constriction of the precapillary segment and (b) decrease in venous return However we are unable to identify the locus of sequestered blood

In other investigations[5,11,17] we have found that ouabain has a direct constrictor effect in the superior mesenteric and carotid arteries of dogs and monkeys Our results with the isolated lung lobe indicate similar responses in the pulmonary artery These data coupled with the rise in arterial pressure and total peripheral resistance identify cardiac glycosides as potent arterial vasoconstrictors in most if not all regional circulations of anesthetized animals

A decrease in venous return with digitalis was reported in the work of Dock and Tainter[5] and was quantified by Cotten and Stopp[4] Our results utilizing flowmeter transducers to measure the output from left and right ventricles indicate that digitalis decreases these outputs by 10 to 20 per cent within a few minutes These findings confirm the measurements of Cotten and Stopp[5] who used a cannulating aortic rotameter The slopes of decline in the outputs of the left and right heart (Figs 1 and 2) indicate no great discrepancy between flows which might implicate the lung as the site of sequestration however our measurement of left heart output excluded coronary blood flow which limits our interpretation of these results We also found that central venous pressure did not increase after injection of the glycoside and that ouabain failed to cause pooling in the isolated lung lobe thereby obviating the likelihood of active trapping of blood in the lung

Our finding of a small rise in portal pressure with ouabain suggests that the splanchnic region is a possible site of trapped blood however previous studies from our laboratory indicated no gain in weight of either gut or spleen and no pooling of blood in the liver[10] The location of the disappearing venous return in the rapidly digitalized dog cannot be identified at present

Table III Comparison of mean pulmonary artery pressure changes in the isolated lower lung lobe after addition of carrier solution alone and then ouabain

Time (min)	Pulmonary artery pressure (mm saline)	
	Solvent alone	*Ouabain added†*
0	194 ± 13 2	183 ± 14 9
2 5	190 ± 13 5	193 ± 14 3‡
5 0	186 ± 12 8	200 ± 16 6‡
10 0	182 ± 12 6‡	209 ± 18 2‡
15 0	184 ± 14 0‡	208 ± 17 9‡
20 0	184 ± 14 [illegible]‡	208 ± 18 2‡

Values p ese t the mean f six expe im nt ± S.E.
†O bai was inj cted t a ously a subsequ t but d n t cal t me seq c after 10 m n t period of st bilization n th sam ix d gs.
‡D ffe s g ifi tly f m co t l val

Summary

Anesthetized dogs with nonfailing hearts were rapidly digitalized with ouabain Aortic blood flow pulmonary blood flow and central venous pressure decreased at approximately equal rates as a function of time Passive congestion of blood in the lung seems unlikely in view of these findings In an isolated lower lung lobe ouabain also failed to cause pooling

Ouabain increased systemic arterial and portal venous pressures and total peripheral resistance as well as increasing pulmonary vascular resistance in the isolated lung lobe These findings indicate that ouabain is a general precapillary constrictor

The author wishes to thank Mr Alvin C K Chang and Mrs Paula Downs for technical assistance and Dr Donald Parker for statistical consultation

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Ventricular responses to hypoxemia following chemoreceptor denervation and adrenalectomy

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There is abundant evidence to support the view that preservation of ventricular function during acute systemic hypoxia is in part attributable to a concomitant elevation in the level of adrenergic stimulation.[1-5] The system or systems responsible for transduction of these responses has not been fully established. Principal consideration has focused on three major areas: the peripheral chemoreceptors, the central nervous system, and release of catecholamines from the adrenal medulla.

It has been suggested that the carotid chemoreceptors are a major sensory system which, when stimulated by reduced oxygen tension, will signal a reflex increase of sympathetic outflow to the heart.[6] However, subsequent studies have failed to support this conclusion.[7,8] Evidence that the carotid chemoreceptors are relatively more important for respiratory regulation and that aortic arch chemoreceptors have a more profound effect on the circulation[10] suggests that the latter may elicit a qualitatively different pattern of autonomic efferent discharge. This idea is consistent with the findings of Stern and Rapaport,[9] who showed that chemical stimulation of aortic arch chemoreceptor tissue with nicotine bitartrate leads to a reflex increase of myocardial contractility, and that this response is reduced or abolished by sectioning the afferent fibers by vagotomy.

In view of the above findings, this study was undertaken in an effort to determine if hypoxic stimulation of the aortic chemoreceptors could be shown to contribute to a reflex increase of adrenergic stimulation of the heart during systemic hypoxemia. A preliminary report on these findings has appeared.[11]

Methods

Adult mongrel cats weighing 2.5 to 3.8 kilograms were anesthetized with intraperitoneal pentobarbital, 30 mg. per kilogram of body weight. A tracheostomy was performed and the cervical vagi were loosely looped. In animals subjected to adrenalectomy, a midline laparotomy was then performed and the right adrenal gland was removed. The left adrenal gland was dissected from the surrounding connective tissue, and a loose ligature snare was placed around its afferent and efferent vessels. The free end of the ligature snare was

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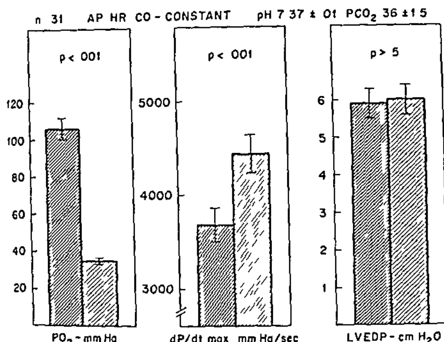


Fig 2 Relationship of arterial oxygen tension (Po) to dP/dt max and left ventricular end diastolic pressure (*LVEDP*) with constant aortic pressure (*AP*) heart rate (*HR*) and cardiac output (*CO*) Average values of 31 responses in 10 animal Vertical brackets indicate standard error of mean Vagi and adrenal glands intact

pressure was controlled by an adjustable constant pressure reservoir

Arterial pH Po_2 and Pco_2 were continuously measured with a Jewett flow through electrode assembly and were frequently checked with an Instrumentation Laboratories system Blood temperature was continuously maintained at 37 ± 1 C by passage through a Sarns heat exchanger Cardiac frequency was held constant by electrical pacing of the left atrium Bilateral carotid body denervation was carried out by sectioning Hering s nerves in selected experiments Aortic body chemoreceptor denervation was achieved by performing bilateral mid cervical vagotomy [10] Desired levels of hypoxia were produced by substituting nitrogen for oxygen in the respiratory gas mixture using a gas mixing device [12]

Changes of ventricular contractility were assessed from the maximal rate of change of left ventricular pressure (dP/dt max)[14] for a given left ventricular end-diastolic pressure (LVEDP) while cardiac output aortic pressure and heart rate were maintained constant The rate of change of left ventricular pressure (dP/dt) was obtained with an unfiltered R C differentiating circuit with a time constant of 0 268 msec This circuit has a frequency response of 100 Hz and a linear phase shift with frequency All animals were given atropine (1 mg) intravenously and changes in left ventricular contractility were compared before and following aortic body chemoreceptor denervation before and after bilateral adrenalectomy and following beta adrenergic blockade with either propranolol or practolol The completeness of beta blockade was confirmed with a test bolus of 0 1 μg of isoproterenol intravenously The data were recorded on a Sanborn 358 direct writing recorder For statistical evaluation of the results the mean values standard errors of the mean and Student s t test values were calculated according to standard methods [1] The differences were considered significant when the P value was less than 5 per cent

Results

Cardiac responses to acute hypoxia with vagi intact Ventricular responses to 31 episodes of hypoxia in 10 atropinized animals

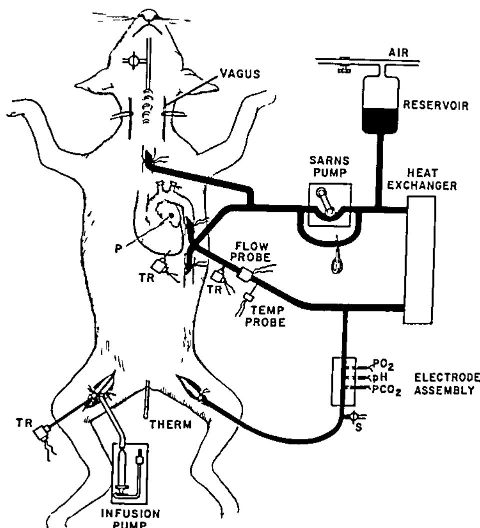


Fig. 1. Semi-diagrammatic representation of preparation used for measurement of ventricular performance under controlled hemodynamic conditions. Left ventricular output was measured with a cannulating type Medicon electromagnetic flow transducer. Pressures were measured in the aortic arch, left ventricle, and femoral artery with Sanborn transducers (*TR*). Cardiac output was controlled with a Sarns roller pump after clamping of the temporary bypass. The pump was set to deliver a constant volume flow approximately equal to that measured prior to clamping of the bypass. Arterial pressure was held constant with a pressurized blood reservoir. Blood samples (*S*) were obtained at frequent intervals for confirmation of blood gas composition and pH. Temperature was controlled with a Sarns heat exchanger in conjunction with a Haake water bath and measured with a Yellow Springs probe in the aortic line and also with a rectal thermometer. *P* = pace electrode.

exteriorized through the abdominal wall. Interruption of the left adrenal circulation was performed by tightening the ligature after the animal was assured reflexic to both systemic hypoxia and temporary central nervous system (CNS) ischemia.[12] Postmortem examination confirmed the adequacy of ligation in all animals.

Respiration was controlled with a Harvard positive pressure pump and a midline thoracotomy was performed. Carbon dioxide was added to the respiratory gas mixture to maintain arterial P_{CO_2} near 35 mm Hg. Heparin (5 mg per kilogram of body weight) was given intravenously. The descending aorta was cannulated and left ventricular output (minus coronary flow) was measured with a Statham cannulating type electromagnetic flow transducer and a Medicon K 2000 flowmeter (Fig. 1). Both the left subclavian and the brachiocephalic arteries were ligated and the latter was immediately cannulated with a branch from the aortic loop. Systemic blood flow was controlled with a Sarns roller pump after clamping the temporary bypass (Fig. 1). Sanborn transducers connected to 15 gauge 1 25 inch stainless steel needles were utilized to measure pressures in the left ventricular chamber and aortic arch. Aortic

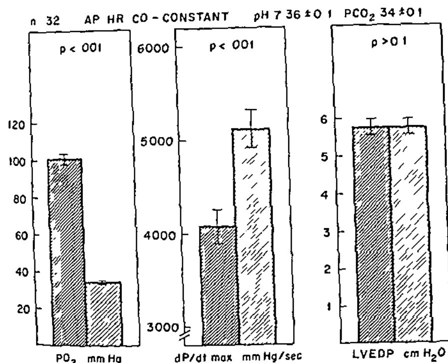


Fig. 4 Average changes of dP/dt max and end-diastolic pressure (*LVEDP*) during systemic hypoxia in 9 animals (32 pairs of studies) following bilateral mid-cervical vagotomy Adrenal glands intact. Vertical brackets show standard error of mean.

bilaterally Following right adrenalectomy but with the left adrenal intact arterial hypoxia (Po_2 35 mm Hg) was associated with an increase of dP/dt max from 2 340 to ?930 mm Hg per second and there was a small reduction in LVEDP Following snare ligation of the left adrenal vasculature re-exposure to hypoxia (Po_2 25 mm Hg) was associated with comparable inotropic changes After bilateral mid-cervical vagotomy the increases of dP/dt max in this animal were somewhat less (approximately 400 mm Hg per second) during hypoxia These responses may be compared to temporary cephalic ischemia produced by interruption of brachiocephalic artery blood flow in which the increase of dP/dt max was approximately 1 ?00 mm Hg per second Following beta receptor blockade with practolol the positive responses to both hypoxemia and cephalic ischemia were virtually eliminated (less than 10 per cent) even though the initial fiber length increased during hypoxia as reflected by the elevation of LVEDP from 5 to 8 cm H O

The data from all of the animals are summarized and compared in Fig 6 before and following vagotomy, and before and following elimination of the adrenal component. When considered in terms of per cent increase of ventricular dP/dt max during acute hypoxemia (mean Po_2 36 ± 1 3 mm Hg) the mean increment was 22 per cent in animals with intact adrenals and vagi and this increment was not changed by vagotomy (Fig 6 top left panel) In animals without adrenals the increase of dP/dt max with acute hypoxia was 20 2 (± 3 6 SEM) per cent before vagotomy Following vagal sectioning the mean increment was somewhat less (15 3 ± 1 5 SEM per cent) but this difference was not statistically significant

In order to determine if the presence or absence of functioning adrenal glands modified the responses the data were further analyzed by comparing responses before and after adrenal removal in animals before vagotomy and after vagotomy (Fig 6 lower panels) With the vagi intact

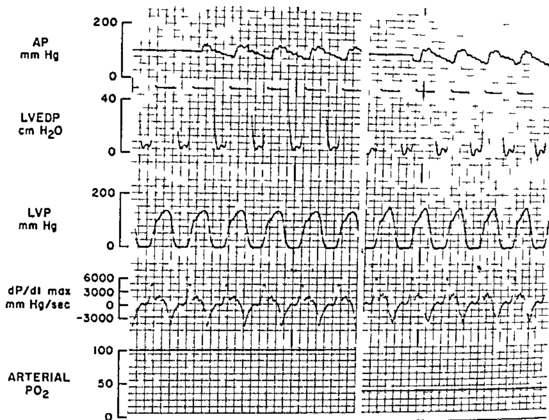


Fig. 3. Original records following bilateral cervical vagotomy showing tracings with normal oxygenation (*left panel*) and during hypoxemia (*right panel*). With constant mean aortic pressure (*AP*) and heart rate (*HR*) end diastolic pressure (*LVEDP*) fell and dP/dt max increased during hypoxia. *LVP* = Left ventricular pressure. Chart speed = 100 mm. per second. Adrenals intact.

with aortic chemoreceptors intact are summarized in Fig. 2. The mean arterial pH during these experiments was 7.37 (± 0.01 SEM) and the mean Pco_2 was 36.4 (± 1.5 SEM) mm. Hg. There was an average fall in Pao_2 from 106 (± 5 SEM) to 35 (± 2.5 SEM) mm. Hg during ventilation with the hypoxic gas mixture. This was associated with a concomitant average increase in dP/dt max from 3,675 to 4,438 mm. Hg per second, an increase of 763 mm. Hg per second ($p < 0.001$). The average LVEDP remained unchanged at approximately 6 cm. H_2O (Fig. 2, right panel).

Cardiac responses to acute hypoxia following bilateral vagotomy. Representative tracings from an animal following vagotomy are shown in Fig. 3. The aortic pressure and heart rate were held constant. When the arterial Po_2 was reduced from 100 to 38 mm. Hg (Fig. 3, right panel) the dP/dt max increased from 4,463 to 5,950 mm. Hg per second, and the LVEDP fell from 4.5 to 3 cm. H_2O. Responses to 32 episodes of hypoxia in 9 animals following vagotomy are summarized in Fig. 4. With an average reduction in arterial Po_2 from 102 to 34 mm. Hg, there was a mean increase in dP/dt max from 4,088 to 5,018 mm. Hg per second, an increase of 930 mm. Hg per second ($p < 0.001$). The average arterial pH was 7.36 and Pco_2 was 34 mm. Hg. The mean LVEDP remained unchanged at 5.8 cm. H_2O (Fig. 4, right panel).

In none of the animals was the response attenuated or abolished by the vagotomy procedure. Similar findings were observed in two cats with prior bilateral carotid sinus and body denervation.

Inotropic responses to acute hypoxia following adrenalectomy. In order to test the possibility that the ventricular responses during acute hypoxia were consequent to either reflex or direct release of catecholamines from the adrenal medulla into the circulation, the adrenal glands in six animals were excised or devascularized as described above. The results from a representative experiment are shown in Fig. 5. The carotid sinus region was denervated

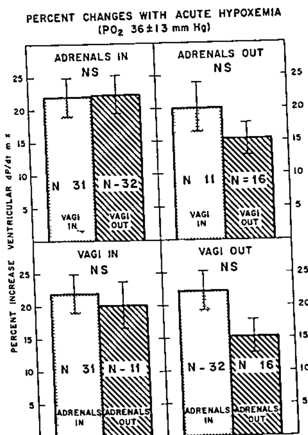


Fig 6 Mean incremental changes of left ventricular dP/dt max before and following adrenalectomy and before and following vagotomy Vertical brackets indicate standard error of the mean The values were assessed for statistical significance using a standard unpaired and unequal sample t test

ity and the end-diastolic pressure It has been shown that dP/dt max is one of the most sensitive measures which indicate changes in force–velocity relations in the intact heart.[16,17] Under carefully controlled hemodynamic conditions with heart rate cardiac output and aortic pressure held constant this measurement faithfully reflects acute changes in the inotropic state of the myocardium Evidence that this is valid in the present study is found in the data from animals following beta adrenergic blockade (summarized in Fig 7) There was no change of dP/dt max during exposure to hypoxemia in animals with or without adrenal function following the administration of either propranolol or practolol Thus it is unlikely that the responses observed prior to beta blockade in the same preparations can be ascribed to mechanical or hemodynamic changes or to other modes of cardiac stimulation such as changes in serum ion concentrations

There is general agreement that most or all of the afferent fibers from the aortic chemoreceptors reach the medullary centers by way of the vagus nerves [10] Hence it is likely that most of the sensory input from these structures would be interrupted by bilateral mid cervical vagotomy The principal objective of this study was to determine the effects of interruption of these fibers on the sympathetic outflow to the myocardium during hypoxia Parasympathetic function was eliminated by atropine administration This obviated the problem of possible changes in ventricular contractility that might result from interruption of efferent vagal discharge following the vagotomy procedures [18]

The results of these experiments have failed to demonstrate a contribution from

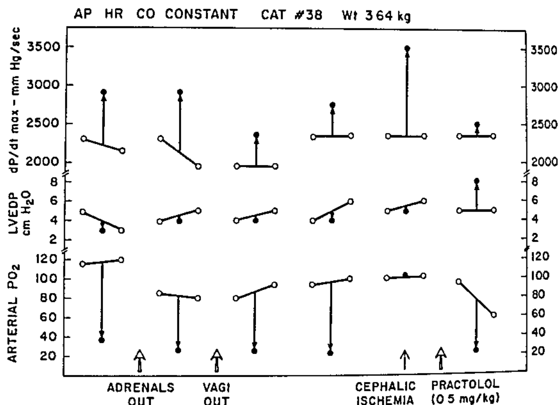


Fig. 5. Sequential measurements of left ventricular performance with normal oxygenation (open circles) and during hypoxemia (closed circles). See text for description of procedures.

(Fig. 6, lower left panel) the average increment of 22.2 per cent did not differ from the 20.2 per cent increase in animals without adrenal glands. In the vagotomized preparations (Fig. 6, lower right panel) there was a somewhat greater difference in the mean per cent increase (22.3 per cent with the adrenals in and 15.3 per cent with the adrenals out). Although these differences suggest a contribution from the adrenal glands in the vagotomized animals, they did not prove to be statistically significant.

Left ventricular responses to hypoxemia following beta adrenergic blockade in seven animals with adrenals intact and in six with bilateral ablation of adrenal function are summarized in Fig. 7. The average dP/dt max with full oxygenation in animals with intact adrenals was approximately 3 700 mm Hg per second. The increase with hypoxemia observed prior to blockade was completely abolished. The average value for LVEDP increased from 7 to 7.5 cm H_2O during hypoxia, but this difference was not significant. Those animals subjected to early removal of adrenal function had a substantially lower dP/dt max with full oxygenation (2 200 mm Hg per second). Beta blockade completely abolished the increase observed prior to blockade. In this group there was a small but significant ($p < 0.01$) increase of end diastolic pressure from 6.5 to 8.2 cm H_2O during exposure to hypoxia. Thus the positive inotropic responses observed in both groups of animals were abolished following beta adrenergic blockade.

Discussion

The findings in the present study are consistent with earlier conclusions that during acute hypoxemia adrenergic stimulation of the myocardium is importantly enhanced in the intact mammal.[1] A primary objective was to explore the mode of transduction of the hypoxic stimulus with major emphasis on the aortic chemoreceptor system. A second objective was to determine if there was an important contribution from the adrenal glands by reflex or direct release of catecholamines into the circulation.

Changes of ventricular contractility were assessed from changes in the maximal rate of pressure rise in the left ventricular cav-

who were able to demonstrate in the mature fetal lamb that stimulation of the carotid chemoreceptors with sodium cyanide elicited cardiovascular responses that could not be reproduced with hypoxemia. They concluded that the difference may be a function of the intensity of the stimulus.

While there appears to be a dichotomy in the response pattern of the two peripheral chemoreceptor groups in that the carotid group may diminish cardiac sympathetic outflow[8,9] while aortic chemoreceptor stimulation may enhance it,[9] the majority of evidence supports the view that the peripheral chemoreceptors are not the only and probably not the most important sensory system responsible for modulation of sympathetic outflow to the heart during hypoxia. A more important source is suggested by the observations of Alexander[1] and of Gellhorn, Cortell, and Carlson.[23] These investigators showed that alterations of blood gas composition within the central nervous system may directly stimulate autonomic centers in the hypothalamus, medulla, and spinal cord.

It is well known that reduced blood flow to the central nervous system elicits an increase of heart rate, myocardial contractility, and peripheral vascular resistance in the adult[14] and in the newborn.[24] This was also demonstrated in the present study and is illustrated in Fig. 5. Baroreceptors have not been identified in the cephalic vessels. This suggested the possibility that the chronotropic and inotropic responses may be related to development of hypoxia and hypercapnia of the autonomic centers when these are deprived of adequate blood flow. It also suggests that these structures may be sensitive to alterations of arterial Po_2 and Pco_2 even in the presence of normal blood flow. This hypothesis has been shown to be correct.[1,23] It appears most likely, therefore, that the sensory system primarily responsible for enhanced sympathetic outflow to the heart during hypoxia as well as hypercapnia resides within the central nervous system and represents an intrinsic functional property of the autonomic centers. The recent work of Krasney[4] suggests that these centers may also be sensitive to histotoxic hypoxia produced by cyanide administration. This provides further evidence to support the concept of central chemosensitivity in cardiovascular autonomic regulation.[14]

Summary

The sensory system responsible for increased ventricular contractility (VC) during hypoxemia is not fully established. Previous studies have demonstrated that isolated carotid body hypoxia is not associated with an increase of VC.[8] However, reflexly increased VC may result from pharmacologic stimulation of the aortic chemoreceptors.[9] In order to evaluate their contribution during hypoxia, VC was studied in atropinized cats before and following denervation by bilateral vagotomy. VC was measured under conditions of constant aortic pressure, cardiac output, and heart rate. Arterial blood gases and pH were continuously monitored. With hypoxemia (Po_2 27 to 46 mm. Hg) all cats showed an increase of VC, manifested by an increase of dP/dt for a given end-diastolic pressure. The responses were unaltered by bilateral vagotomy. Similar findings were obtained in animals with bilateral carotid body denervation. The increase of VC during hypoxia was not significantly less following adrenalectomy. Beta adrenergic blockade completely abolished these responses. It is concluded that the increase in VC associated with systemic hypoxia cannot be entirely attributed to aortic or carotid chemoreceptor reflex activity. The influence of stimulation of structures within the central nervous system must also be considered.

The technical assistance of Mr. Ronald Gordon and Mr. Victor Hardaswick is gratefully acknowledged.

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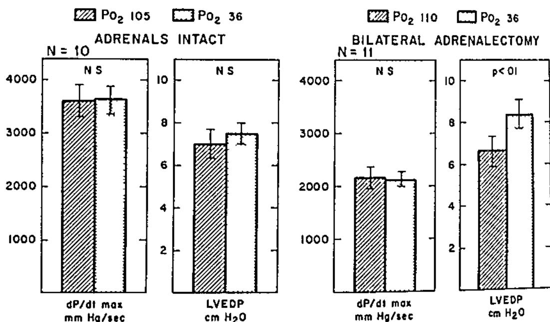


Fig. 7. Left ventricular responses to hypoxemia following beta adrenergic blockade in animals with intact adrenal glands (*left panels*) and following bilateral adrenalectomy (*right panels*). Vertical brackets indicate standard error of the mean. Positive inotropic responses were completely abolished. In the adrenalectomized animals there was a small but significant increase of end diastolic pressure (*LVEDP*) during hypoxia ($p < 0.01$).

hypoxic stimulation of the aortic chemoreceptors to the recorded increments of dP/dt max. With the afferent fibers intact, reduction of the arterial Po_2 to 35 mm. Hg was associated with a 22.2 (± 2.9 SEM) per cent increase of dP/dt max. Following bilateral vagotomy the same level of hypoxemia induced a 22.3 (± 3.0 SEM) per cent increase. These findings are consistent with earlier electroneurographic observations[7] which demonstrated large increments of impulse traffic in the inferior cardiac branch of the stellate ganglion during exposure to acute hypoxia. Equally large increments were observed following bilateral sectioning of the vagi and Hering's nerves. These findings therefore do not support the concept that stimulation of peripheral chemoreceptors is essential to modulation of sympathetic outflow to the heart in systemic hypoxia.

The adrenal glands provide another potential source for adrenergic stimulation of the myocardium through the release of increased amounts of catecholamine into the circulation. It is unlikely, however, that sufficient norepinephrine could be obtained from this source to provide detectable changes in ventricular performance during acute hypoxia.[19] This idea is consistent with present findings in which the increment of dP/dt max was 20.2 (± 3.6 SEM) per cent following removal of adrenal function compared with an increment of 22.2 (± 2.9 SEM) per cent with adrenal function intact ($p > 0.8$). The effect of adrenalectomy appeared to be somewhat greater in the vagotomized animals in that the increase of dP/dt max was 15.3 (± 2.5 SEM) per cent, but this difference did not prove to be statistically significant (Fig. 6, lower right panel). It is more likely that the lower average value is attributable to the additional surgical manipulations incident to the adrenalectomy procedures.

The work of Stern and Rapaport[9] has shown that chemical stimulation of receptors in the region of the aortic arch can reflexly increase cardiac contractility and that the afferent limb of the reflex arch is carried in the vagus nerves. The present studies do not preclude the possibility that hypoxic stimulation of aortic chemoreceptor tissue may contribute to the positive inotropic responses seen in systemic hypoxia. It does seem clear, however, that the cardiac responses are undiminished in the absence of afferent input from this source.[0] Thus a parallel may be drawn with the observations of Dawes and associates[11]

Case reports

External left atrial pulse tracings in extreme left atrial dilation

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Considering the frequency of rheumatic disease of the mitral valve, extreme left atrial dilation is a rare condition. The enlarged chamber may easily be mistaken for right pleural effusion with the potential hazard of aspiration.[1,2] Clinical recognition is not easy and sometimes thoracotomy has been performed to establish the diagnosis.[3] Patients with extreme left atrial dilation present with a rather characteristic spectrum of physical signs, of which the presence of systolic pulsations of the right anterior chest wall attributed to the left atrium is considered the most characteristic. The present report deals with the recording of these pulsations which form a valuable diagnostic tool.

Case reports

Case 1. A 34-year-old woman was first seen in April, 1967, because of moderate limitation of effort tolerance. There was a history suggestive of rheumatic fever at the age of 9, with recurrent attacks of arthralgia for the next few years. When the patient was 12 years old, a cardiac murmur was heard and a tonsillectomy was performed. Attacks of paroxysmal nocturnal dyspnea occurred infrequently and severe hemoptysis occurred once. A stitchlike chest pain, localized to the right axilla but frequently referred to the right shoulder, began one year prior to admission but subsided a few months later. The patient mentioned a slight dysphagia on swallowing but said that it caused her little trouble.

On examination the patient was found to be slightly underdeveloped and in no apparent distress. The jugular venous pulse was elevated 2 to 3 cm. above the sternal angle; there was atrial fibrillation and the blood pressure was 130/80 mm. Hg. The liver was enlarged two fingerbreadths below the right costal margin and there was slight ankle edema. Chest examination revealed a small thoracic cage and a marked precordial bulge.

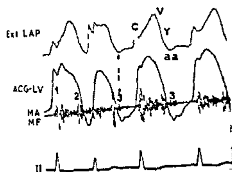
Cardiologic examination showed a heaving apical impulse in the seventh space in the anterior axillary line and a palpable third heart sound. There was a moderate parasternal heave. Systolic expansion of the right anterior thoracic wall was both visible and palpable. Cardiac dullness extended to the right anterior axillary line and there was dullness on the lower right lung base. Auscultation revealed a holosystolic murmur Grade 4/6 over the apex with a loud third heart sound and a short mid-diastolic murmur. The systolic murmur was widespread and could be heard clearly on the right side and on both lung bases. The electrocardiogram (ECG) showed coarse fibrillatory waves, right axis deviation, and high voltage of the R waves in the left surface leads. A chest roentgenogram revealed a greatly enlarged cardiac shadow that touched the chest wall on both the left and right sides (Fig. 1). There were lines of old pleural reaction on the right side. The esophagus was displaced posteriorly and to the left with marked angulation in the left lateral view (Fig. 2). Fluoroscopy showed vague pulsations of the right cardiac border.

With the patient in the supine position, the right

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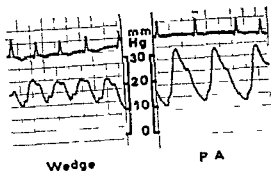


F 3 Case 1 External left atrial pulse tracing (*Ext LAP*) recorded simultaneously with left ventricular apexcardiogram (*ACG-LV*) and PCG at mitral area *1 2* and *3* First, second and third heart sound *C V* and *V* left atrial c and v waves and v descent *aa* annular descent point *MA* mitral area, *MF* medium frequency

especially prominent in the third and fourth intercostal spaces in the right midclavicular line The cardiac dullness extended beyond the right midclavicular line and there was dullness on the right posterior lung base Auscultation over the apex revealed a holosystolic murmur Grade 4/6 followed by both a sharp opening snap and a loud third heart sound A short high pitched mid diastolic murmur was localized over the apex but the systolic murmur was widely propagated to the right of the sternum anteriorly and to both lung bases posteriorly The ECG showed atrial fibrillation with coarse fibrillatory waves and a QRS pattern consistent with left ventricular hypertrophy A chest roentgenogram revealed a markedly enlarged cardiac shadow The cardiac border extended to within ? cm of the right chest wall (Fig 5) The esophagus was markedly displaced to the left and posteriorly Fluoroscopy demonstrated a vigorous pulsation of the left cardiac border and minimal pulsation of the right border

The right thoracic pulsations were recorded in the third intercostal space in the midclavicular line simultaneously with the left ventricular ACG and the PCG at the mitral area (Fig 6) The pulse wave contour was typical of the left atrial pulse tracing of mitral regurgitation. The curve consisted of a positive CV wave with a rapid Y descent. The C wave was recorded synchronously with the first heart sound in the PCG The opening of the mitral valve was defined in the tracing by both the O point of the left ventricular ACG and the high pitched vibrations of the opening snap in the PCG The peak of the V wave showed a rapid decline to the aa point which was synchronous with the peak of the rapid filling wave (RFW) of the left ventricular ACG and the vibrations of the third heart sound in the PCG Immediately following the aa point the left atrial pulse tracing showed a rapid rise marking the wave of diastasis that continued until the next C wave

On venous catheterization the pulmonary artery was entered but the catheter failed to advance to a wedge position it always coiled in the right atrium.



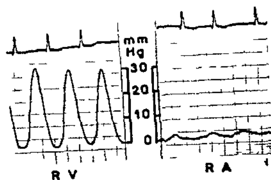


Fig 4 Case 1 Pressure tracings recorded during venous catheterization. *PA* Pulmonary artery *RV* right ventricle *RA* right atrium.



Fig 5 Chest radiograph P A view of second case



Fig. 1 Chest radiograph P A view of first case

anterior thoracic pulsations were recorded from the fourth intercostal space in the anterior axillary line with the use of a pick up bell secured in place by a rubber strap simultaneously with the left ventricular apexcardiogram (ACG) and the phonocardiogram (PCG) at the mitral area The recordings were made on a four channel Mingograph type 42B at a paper speed of 50 mm per second (Fig 3) The tracing revealed a pulse wave contour typical of left atrial pulse tracings in the presence of mitral regurgitation There was a positive CV wave with a rapid Y descent The C wave was synchronous with the high pitched components of the first heart sound in the PCG and corresponded to a notch on the ascending limb of the left ventricular ACG The V wave showed a rapid decline to a point (aa) marking the annular ascent point [4] This point was synchronous with the third heart sound

Venous catheterization revealed a moderately elevated wedge pressure The pulmonary artery pressure and the pulmonary arteriolar resistance were only slightly above normal limits (Fig 4 and Table I) A diagnosis of dominant mitral regurgitation with extreme left atrial dilation was made and the patient was discharged on maintenance doses of digitalis and diuretic therapy

The patient was readmitted in December 1968 with dysphasia and right embolic hemiplegia and was given anticoagulants The dysphasia rapidly regressed but the motor power showed only slight improvement On the eighteenth day following admission the patient suffered a sudden attack of severe dyspnea with frothy blood tinged sputum Drowsiness and hypotension soon followed and the patient died two hours later

Postmortem examination revealed an enormously enlarged heart that almost filled the entire chest The main chamber was the left atrium which was markedly dilated and contained more than 2 L of blood It showed close contact with the right thoracic wall especially on the anterior and lateral



Fig 2 Chest radiograph left lateral view of first case

aspects The wall was thin and fibrous and was no more than 1 mm thick The endocardium showed calcification especially prominent in the auricular appendage but there was no mural thrombosis The right atrium was about one third the size of the left with the endocardium showing patchy calcification and hypertrophied pectinate muscles The left ventricle was markedly dilated and hypertrophied and measured 1 5 cm in thickness the right ventricle also dilated measured 0 5 cm The mitral valve was heavily calcified showing severe regurgitation with slight stenosis at the commissures the circumference measured 35 mm Microscopic examination of the left atrium showed marked fibrosis of the wall with very few muscle fibers and scattered Aschoff bodies

Case 2 A 35 year old man was admitted to the hospital in January 1969 complaining of dyspnea on moderate exertion frequent attacks of paroxysmal nocturnal dyspnea and a persistent cough with bronchospasm He had had rheumatic arthritis at the age of 13 and it had recurred several times in subsequent years

Examination revealed a well nourished man in no apparent distress The jugular venous pulse was slightly raised Atrial fibrillation was detected in the pulse and the blood pressure was 130/85 mm Hg The liver was enlarged one fingerbreadth below the right costal margin and there was slight edema around the ankles The chest was small with a moderate precordial bulge

Cardiologic examination showed a heaving apical impulse in the sixth space in the anterior axillary line with a loud palpable third heart sound followed by a short diastolic thrill Systolic pulsations were evident on the right anterior thoracic wall and were

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ening of the mitral valve to the aa point which was synchronous with the peak of the RFW of the left ventricular ACG and the third heart sound in the PCG. Immediately following the aa point the left atrial pulse tracing showed a rapid rise marking the wave of diastasis that continued until the next C wave.

Venous catheterization revealed a moderately raised wedge pressure The pulmonary artery pressure and the pulmonary arteriolar resistance were slightly above normal limits (Table I) The patient was found to have severe mitral regurgitation with extreme left atrial dilation and was advised to have a mitral valve replacement but she refused the operation and was later discharged on maintenance doses of digitalis and an oral diuretic.

In October 1970 the patient three months pregnant, was admitted for a medically induced abortion. Although the operation was completed uneventfully the patient developed severe bleeding 12 hours later with marked hypotension Resuscitation failed

On postmortem examination the heart was found to occupy no less than 80 per cent of the thoracic cavity with marked compression of both lungs The main cardiac chamber was the left atrium which occupied the entire right hemithorax in close contact with the thoracic cage on the anterior lateral and posterior aspects. The left atrium was dilated contained 2 8 L. of blood and had a fibrous wall no more than 1 mm thick. The right atrium was moderately dilated and contained multiple postmortem thrombi The left ventricle was hypertrophied and dilated and its wall was 13 mm thick. The wall of the right ventricle was 5 mm thick. The mitral valve showed marked fibrotic deformity the free margins of the cusps were rolled rigid and calcified. The circumference of the valve was 43 mm or 3½ fingerbreadths. Microscopic examination of the left atrium showed marked fibrosis of the wall with almost complete replacement of the muscle fibers.

Discussion

This report presents for the first time external recordings of right thoracic pulsations in three patients with rheumatic mitral regurgitation and extreme left atrial dilation The pulsations were attributed to the fact that the enormously dilated left atrium was in close contact with the right thoracic wall This study was conducted following an earlier observation of marked pulsation of the right anterior thoracic wall in a patient with rheumatic mitral regurgitation and extreme left atrial dilation In this case external tracings were not recorded The patient died following a massive pulmonary embolism and postmortem examination showed the markedly dilated left atrium coming in close contact with the right thoracic wall for a considerable area


Fig 7 Chest radiograph P A view of third case

In the following three years three more cases were discovered

These patients present with a rather characteristic spectrum of physical signs that can frequently establish the diagnosis The minimal evidence of congestive failure when first seen the consistent finding of atrial fibrillation the displaced and heaving apical impulse dominant mitral regurgitation and the wide spread of the systolic murmur to both lung bases and to the right anterior thoracic wall were common findings in our cases Most characteristic among the physical signs is the extension of the cardiac dullness to the right of the sternum frequently as far as the axillary line with both visible and palpable pulsations in these areas This dullness together with the dullness at the right posterior lung base have led to the erroneous diagnosis of right pleural effusion in some cases [3] The dullness and pulsations are attributed to the dilated left atrium This rightward extension of left atrial dullness is explained by the anatomy of this chamber where the line of least resistance for left atrial dilation is rightward with both anterior and posterior extensions [2,3]

In contrast to the characteristic physical signs the symptomatology is not usually diagnostic In fact some of the previously mentioned characteristic symptoms such as right sided chest pain have received various descriptions and explanations fre

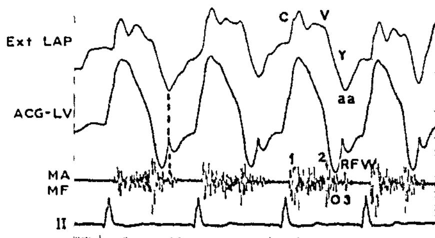


Fig. 6 Case 2 External left atrial pulse tracing (*Ext LAP*) recorded simultaneously with left ventricular apexcardiogram (*ACG LV*) and PCG at the mitral area *1 2* and *3* First second and third heart sounds *C V* and *Y* left atrial c and v waves and y descent *aa* annular ascent point *O* stands for both the O point of the ACG LV and the opening snap of the PCG *RFW* rapid filling wave *MA* mitral area *MF* medium frequency

The pulmonary artery pressure was slightly elevated and the cardiac output was diminished (Table I) In a later attempt the left ventricle was approached percutaneously from the right femoral artery entry into the left atrium was attempted but failed The patient was maintained on digitalis and diuretic therapy and showed marked response In August 1969 the patient died shortly after a non cardiac surgery A postmortem report mentioned that the left atrium was extremely enlarged extending into the right hemithorax and coming in close contact with a considerable area of the right anterior thoracic wall The right atrium was moderately dilated The walls of the right and left ventricles were 5 and 12 mm thick respectively The mitral valve was markedly regurgitant with an opening of 3½ finger breadths

Case 3 A 27 year old woman was first seen in September 1969 complaining of moderate limitation of effort tolerance occasional attacks of paroxysmal nocturnal dyspnea mild orthopnea and recurrent chest infection with bronchospasm She had had her first attack of rheumatic arthritis at the age of 9 years and since then she had experienced several other attacks A cardiac murmur was first discovered at the age of 11 and soon afterward the cardiac symptoms began The patient was married at the age of 18 and her first pregnancy and labor took place at the age of 20 with little discomfort Congestive failure developed during the third trimester of her second and third pregnancies at ages 22 and 25 respectively The congestive failure regressed rapidly after labor and the patient had been irregularly receiving antifailure therapy for the 2 years preceding this admission

Examination revealed a well nourished woman in no apparent distress The jugular venous pulse was raised 2 to 3 cm above the sternal angle Atrial fibrillation was detected in the pulse the blood pressure was 120/80 mm Hg bilaterally The liver was palpable one fingerbreadth below the right costal margin there was no ankle edema Chest examination revealed a thoracic cage of moderate size with an evident precordial bulge

Cardiologic examination showed a heaving apical impulse displaced to the seventh space in the anterior axillary line with a palpable third heart sound There was a moderate parasternal heave Systolic pulsations were both seen and felt on the right anterior axillary and lower posterior thoracic wall with clear systolic expansion of the anterior part of the right hemithorax The cardiac dullness extended to the whole right hemithorax on the anterior axillary and lower posterior sides Auscultation revealed a holosystolic murmur Grade 4/6 on the apex with a loud third heart sound and a short mid diastolic rumble The systolic murmur was widespread and could be clearly heard on the whole right side of the chest The ECG showed coarse fibrillatory waves right axis deviation and a moderate degree of clockwise rotation in the precordial leads The chest roentgenogram revealed a greatly enlarged cardiac shadow that touched the chest wall on both the left and right sides (Fig 7) The left lateral view showed displacement of the esophagus posteriorly and to the left with marked angulation

Fig 8 illustrates the simultaneous recording of cardiac pulsations from a point at the fifth space in the right midaxillary line (the external left atrial pulse tracing) and a point at the seventh space in the left anterior axillary line (the left ventricular ACG) together with the PCG at the mitral area The tracing obtained from the right thoracic wall revealed a pulse wave contour typical of left atrial pulse tracings in the presence of mitral regurgitation The curve consisted of a positive C wave with a rapid Y descent The C wave was synchronous with the high pitched components of the first heart sound From the V peak the curve declined in the Y descent which consisted of three phases The first phase was a decline which extended from the peak of the V wave to the O point of the left ventricular ACG which marked the opening of the mitral valve The second phase was a rapid fall from the time of the

gurgitation may show not only freely pulsating neck veins and a pulsating liver but also a massive pulsation of the right side of the chest that yields almost square waves which may superficially simulate those demonstrated in the present study However the question of differentiating the right thoracic pulsations in patients with extreme left atrial dilation does not seem to be a major problem in many of these cases there is slight or no evidence of tricuspid regurgitation when first seen In our four patients with extreme left atrial dilation evidence of significant tricuspid regurgitation was uniformly absent on the first examination when the right thoracic pulsations were initially detected The jugular venous pulse was slightly raised and the liver was only one or two finger breadths enlarged Hemodynamic studies in all cases showed consistently normal end-diastolic pressure of the right ventricle and normal right atrial pressure (Table I and Fig 4) The finding of right thoracic pulsations in a patient with severe mitral regurgitation but with minimal evidence of tricuspid regurgitation should immediately raise the possibility of marked left atrial dilation

Analysis and correlation of intracardiac left atrial pulse tracings in mitral valve disease with the underlying hemodynamic disturbances and with events in the cardiac cycle and the PCG have been frequently reported[8,10] This work however gives the first description of such correlation using an external left atrial pulse tracing and proves that the external tracing reflects the same qualitative changes in the left atrial pressure although it lacks the quantitative value. The external left atrial pulse tracing will aid in determining which type of mitral valve lesion is present Although dominant mitral regurgitation is the most frequent underlying factor and therefore the external left atrial pulse tracing will be consistent with this hemodynamic disturbance yet in the uncommon instances in which dominant mitral stenosis is present the external left atrial pulse tracing will prove characteristic Observation of our difficulty in advancing the catheter to a wedge position in the second case and the failure of our attempt to enter the left atrium because of the marked change in the anatomic relationship will make the external left atrial pulse tracing most valuable in some of the cases

The external recording of direct left or right atrial pulsations has not been previously reported In a recent study of the left parasternal pulsations as represented by the right ventricular ACG in cases of rheumatic tricuspid stenosis we found a prominent presystolic a wave which was not observed in the right ventricular pressure pulse The size of the a wave was found *to correlate fairly well with the calculated* tricuspid valve area Since the wave could not be explained as a result of the right atrial contraction causing the blood to enter the ventricle leading to change in the right ventricular end-diastolic volume (as in the case of pulmonary hypertension for example) it was feasible to consider it representative of direct right atrial tracing as sensed by the recording piece applied at the left sternal border[11]

Extreme left atrial dilation with right thoracic pulsations is a rare condition In the last three years we have found only four cases among the 120 patients with dominant mitral regurgitation admitted during that period (3 3 per cent) No patient with mitral regurgitation with moderate left atrial dilation showed right thoracic pulsations which is consistent with the anatomic considerations of the disease On the other hand none of the 242 patients with mitral stenosis seen in the same period showed extreme left atrial dilation or right thoracic pulsations Most of those reported to have extreme left atrial dilation had mitral regurgitation[2] however on rare occasions mitral stenosis may be associated with rather large atria[12]

The presence of systolic pulsations of the right anterior thoracic wall was reported infrequently in the early cases of extreme left atrial dilation In a later publication Sloan and associates[3] stressed its diagnostic value in their three patients with massive dilation of the left atrium Although De Sanctis Dean and Bland[2] reported the pulsations in only one of their ten patients with extreme left atrial dilation yet in two others there were systolic pulsations of the right posterolateral chest wall The relatively infrequent reporting of these pulsations may be ascribed to variations in a

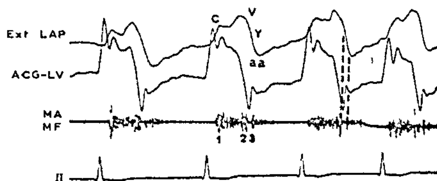


Fig 8 Case 3 External left atrial pulse tracing (Ext LAP) recorded simultaneously with left ventricular apexcardiogram (ACG LV) and PCG at the mitral area 1, 2 and 3 First second and third heart sound C V and Y left atrial c and v waves and y descent aa annular ascent point MA mitral area MF medium frequency

Table I Hemodynamic data in three cases of extreme left atrial dilation

Case No	Wedge (mm Hg)	PA* (mm Hg)	RV (mm Hg)	RA (mm Hg)	CO (L/min)	PAR (dynes sec cm⁻⁵)
1	22/13(17)	32/11(21)	32/0	3/0	3 2	100
2	—	38/18(26)	38/3	4/1	4 2	—
3	23/12(16)	34/15(22)	34/2	5/2	3 5	137

*PA pulmonary artery RV right ventricle RA right atrium CO cardiac output and PAR pulmonary arteriolar resistance.

quently with little rationale [2,3,5] The right sided chest pain of our patient was thought to be pleuritic in origin On the other hand mild dysphagia was discovered in one patient and only by means of direct questioning The rarity of embolization previously mentioned[2] contrasts with its presence both in our early case of extreme left atrial dilation and in the first case in this report although in the former case the embolization was right sided and only in the second case can we implicate the enlarged left atrium However there was no evidence of mural thrombosis at postmortem examination The only characteristic feature of these patients may be the observed discrepancy between the fair degree of effort tolerance and the degree of cardiac enlargement attributed mainly to the left atrial dilation

The recording over the right thoracic wall of a pulse wave contour consistent with left atrial pulse tracing is not an unexpected finding in view of the anatomic considerations of the disease In our four cases with extreme left atrial dilation, the enormously dilated atrium was shown in postmortem examination to have close contact with a wide area of the right thoracic wall In the three patients in whom external tracings were obtained the recording piece was applied to an area of the right thoracic wall that was later shown to have close contact with the left atrial chamber An important indication that we are dealing with genuine left atrial pulse tracings is provided by analysis of the contour of the curve and its timing which are characteristic in relation to the left ventricular hemodynamic events as represented by the left ventricular ACG and the auscultatory phenomena as revealed by the PCG at the mitral area

Although it may be questioned whether we are dealing with a true pressure curve or a volume curve it is probable that in the markedly dilated left atrium the pressure and the volume rise and fall together

It may be argued that right thoracic pulsations are caused by tricuspid regurgitation Patients with severe tricuspid re

Postural hypotension in amyloid disease

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Postural hypotension may occur during the course of primary amyloidosis[1-5] usually in association with other signs and symptoms of autonomic dysfunction and peripheral neuropathy It has been assumed to be due to autonomic involvement but it has never been investigated and its pathophysiological mechanism has not been established

In this report we describe a patient with primary amyloidosis who presented with the nephrotic syndrome and subsequently developed incapacitating postural hypotension He had no other manifestations of autonomic disturbance and no clinical evidence of peripheral neuropathy Hemodynamic studies were performed and the results correlated with the pathological findings.

Case report

A 61 year-old man was admitted to the Department of Medicine Manchester Royal Infirmary in November 1964 For ten months he had complained of generalized ill health loss of appetite excessive tiredness, and progressive swelling of the legs. He had had lack of effort and moderate dyspnea on exertion for about two years. His past and family history were noncontributory

On examination he looked pale and had extensive pitting edema of the legs and sacral region The pulse was 82 beats per minute and regular the blood pressure was 110 80 mm. Hg the heart sounds were normal and there was no elevation of the jugular venous pressure Examination of the respiratory system and abdomen yielded negative results No abnormality was detected in the nervous system in particular the tendon jerks were brisk and symmetrical and there was no superficial or proprioceptive sensory impairment. There was no detectable thickening of peripheral nerves.

Laboratory investigations The hemoglobin was 15 ? Gm per 100 ml the white blood cell count was 11 400 per cubic millimeter the erythrocyte sedimentation rate was 10 mm in 1 hour (Wintrobe) the platelet count was 242 000 per cubic millimeter the reticulocyte count was 2 per cent.

The urinary protein excretion in 24 hours was 13 Gm the serum albumin was 1 9 Gm per 100 ml the serum globulin was 1 8 Gm per 100 ml electrophoresis showed a slight increase in the alpha ? globulins with marked reduction of the gamma globulins the blood urea was 25 mg per 100 ml the serum electrolytes were within normal limits (serum cholesterol 330 mg per 100 ml serum calcium 8 6 mg per 100 ml serum inorganic phosphorus 4 ? Gm per 100 ml serum creatinine 1 0 mg per 100 ml urea clearance 49 ml per minute creatinine clearance 120 ml per minute)

Examination of the urine revealed 50 pus cells per high power field and a growth of *Escherichia coli* this infection responded to ampicillin and did not recur *An intravenous pyelogram did not reveal any* abnormality

The antistreptolysin O titer was less than 50 Todd units results of the lupus erythematosus test antinuclear factor sensitized sheep cell and F II Latex tests were repeatedly negative

The glucose tolerance test result was normal and the Wasserman Reaction was negative

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number of parameters including, in particular, the degree of left atrial dilation and its anatomic characteristics especially the degree of extension in the anterior direction in relation to the size and anatomy of the thoracic cage. Our first two patients had small thoracic cages.

The recording of external left atrial pulse tracings of classical mitral regurgitation in patients with extreme left atrial dilation may prove that the distensibility and pressure characteristics of a markedly dilated left atrium do not differ to any appreciable degree from those of the moderately dilated left atrium commonly encountered. This distensibility enables the markedly dilated left atrium to "absorb" both the large ventricular regurgitant jet and the raised diastolic pressure of a failed ventricle and in a way, to protect the pulmonary vascular bed from the effect of raised pressure. Our finding of slightly elevated pulmonary artery pressure and normal pulmonary arteriolar resistance favors this hypothesis.

Summary

In three cases of extreme left atrial dilation in patients with rheumatic mitral regurgitation, while the symptomatology was nonspecific, the clinical examination offered a rather characteristic spectrum of physical signs, most significant of which was the presence of systolic pulsations of the right anterior thoracic wall attributed to the dilated left atrium. The recording of these pulsations showed a pulse wave contour exactly similar to the intracardiac left atrial pulse tracing in mitral regurgitation. It is suggested that the tracing can help in the diagnosis of both extreme left atrial dilation and of the nature of the underlying mitral valve disease.

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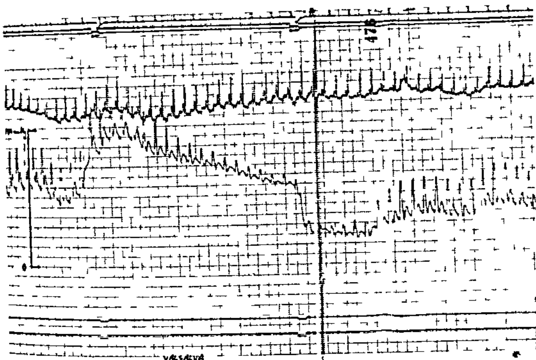


Fig 2 The ECG (upper tracing) and intra arterial pressure record (lower tracing) during Valsalva s maneuver The pressure scale is shown on the left. The time marker at the top of the tracing gives 1 sec intervals.

Table I Hemodynamic findings

Heart rate (per min.)	*Cardiac output (L/min)*	*Blood pressure (mm Hg)*			*Right atrial pressure (mm Hg)*	*Peripheral resistance (units)*
		Systolic	*Diastolic*	*Mean*		
Lying						
96	2 2	84	54	62	3	28
96	2 2					
96	2 3					
96	2 3					
96	2 2					
Standing						
95	2 0	55	41	46	—	23

Hemodynamic investigations The heart rate arterial pressure central venous pressure and cardiac output were measured The heart rate was determined from a continuous recording of the ECG Using the Seldinger technique a 55 cm. piece of FG4 (Portex Ltd) tubing was inserted percutaneously into the right brachial artery and advanced under x ray screening control to the aortic root. This tube was used to measure central arterial pressure and to withdraw arterial blood for cardiac output determinations. A similar piece of FG4 tubing was inserted percutaneously into the right antecubital vein and advanced into the right atrium to measure the central venous pressure and to inject dye for cardiac output determination Pressures were measured with a P23Gb Statham transducer using a Sanborn carrier amplifier and a Mingograph 81 (Elema) Recorder The cardiac output was determined by the dye dilution technique using the Waters X 301 densitometer and cuvette and a Gilford withdrawal pump

Measurements were taken with the subject lying down and standing and the subject performed Valsalva s maneuver while lying The results are shown in Table I and Fig 2

The cardiac output was low in the presence of a

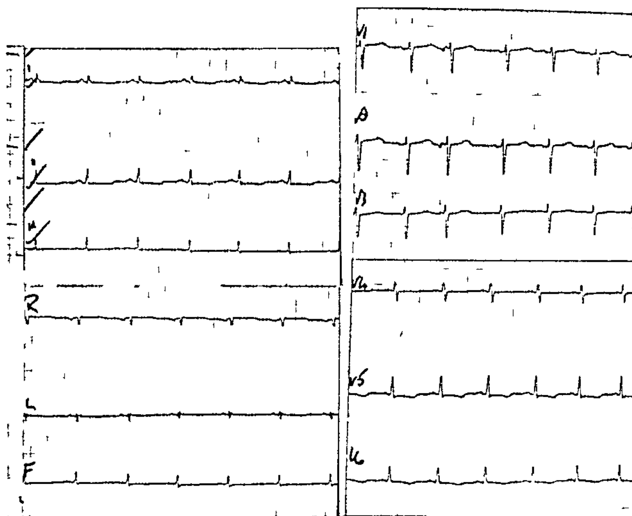


Fig. 1. The patient's ECG

A chest x-ray revealed small healed tuberculous foci at the left apex; the rest of the lung fields was clear and the cardiac shadow was normal. The electrocardiogram (ECG) showed small QRS complexes and flattening or inversion of T waves in most leads (Fig. 1).

The prothrombin time of a control subject was 12.5 seconds; that of the patient was 17 seconds. This prolongation of the prothrombin time was further investigated and was found to be due to a mild factor VII deficiency and did not respond to intramuscular injections of vitamin K_1.

The serum bilirubin, thymol turbidity, alkaline phosphatase, serum glutamic oxalacetic transaminase, and serum glutamic pyruvic transaminase were within normal limits.

A bromsulphthalein test showed 40 per cent retention at 30 minutes and 25 per cent retention at 45 minutes. A renal biopsy contained about 36 glomeruli, the majority of which showed no abnormality. A few glomeruli revealed small focal deposits of amorphous material in the mesangial stalk which gave a faintly positive reaction with Congo red. The arteries, tubules, and interstitium showed no abnormality. A rectal biopsy did not reveal evidence of amyloid disease.

Treatment and progress. The patient was treated with bed rest, a high protein–low salt diet, and diuretic therapy without any significant response. A short course of prednisolone given at another hospital during the early course of the disease had been without effect. He was discharged from the hospital in December of 1967.

A few weeks later he attended the outpatient clinic complaining of postural dizziness and fainting attacks and was found to have marked postural hypotension with a blood pressure of 110/70 mm Hg lying down and 75/0 standing. He was readmitted on February 15, 1968. Apart from the severe postural hypotension, the physical signs were as noted on his previous admission. There were no signs of cardiac failure and repeated examination of the nervous system was negative. An autonomic neuropathy was suspected and this view was supported by the results of the hemodynamic studies. The postural symptoms became so severe that the patient was unable to sit or stand. He developed an infected necrotic ulcer on the lower lip which was complicated by septicemia with β-hemolytic streptococci to which the patient succumbed despite treatment on March 10, 1968. His blood urea remained normal throughout the course of his illness until a few days prior to his death, when it rose to a maximum level of 60 mg. per 100 ml.

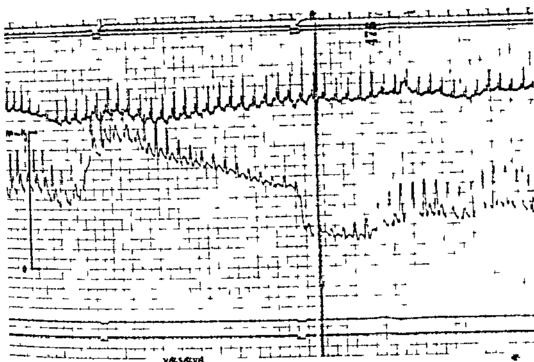


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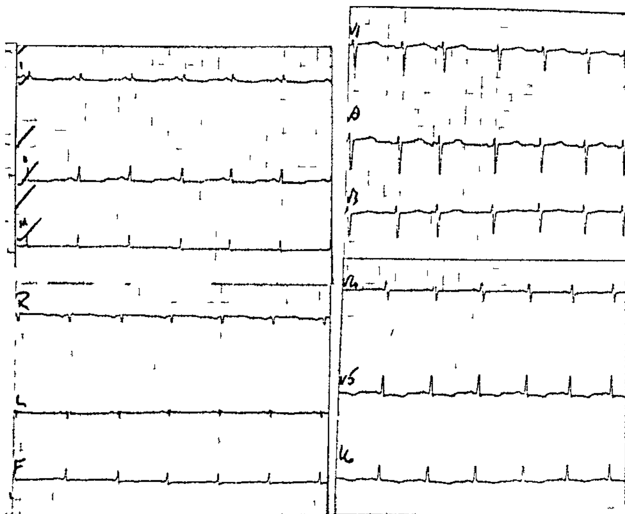


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Fig 3 Part of a thoracic sympathetic ganglion with an efferent branch showing infiltration with amyloid (Hematoxylin and eosin × 480)



Fig 4 A lumbar nerve trunk containing amyloid deposits. (Hematoxylin and eosin × 380)

134 published cases[8] diarrhea was present in 15 per cent and neurological involvement in 13 6 per cent

Postural hypotension in amyloid disease has never been investigated hemodynamically it has been presumed to be due to autonomic neuropathy but in some cases has been ascribed to myocardial involvement. In our patient postural hypotension was the only manifestation of autonomic involvement and this occurrence in the absence of any clinical signs of peripheral neuropathy has been reported only once previously[2] The severity of the hypotension was responsible for the giddiness and fainting attacks Mild or moderate degrees of orthostatic hypotension may however be present without producing any symptoms and this sign which may be the only manifestation of autonomic neuropathy may be missed unless especially looked for

The place of the Valsalva maneuver in demonstrating autonomic dysfunction as a cause of orthostatic hypotension is now well established[10 14] In healthy subjects the acute rise in intrathoracic pressure impedes venous return and produces a fall in stroke volume and pulse pressure and ultimately a decrease in the systolic and diastolic pressures This stimulates baroreceptors in the carotid sinus and aortic arch leading to reflex vasoconstriction which stops any further drop in the blood pressure and persists after release of the intrathoracic pressure leading to an overshoot of the blood pressure above the original level and to reflex bradycardia These responses are absent in patients with autonomic neuropathy and were not observed in our patient The absence of any alteration in the pulse rate on standing and during and after the Valsalva maneuver is evidence of impairment of the positive and negative chronotropic nervous drive to the heart and it is likely that the fixed heart rate (96 per minute) represents the intrinsic rate of the sinoatrial node This patient thus showed evidence of central and peripheral autonomic cardiovascular denervation

The cause of the amyloid neuropathy was originally ascribed to metabolic factors[15] or to ischemic degeneration secondary to vascular involvement by amyloid substance[7 16 17] However pathological studies have clearly demonstrated as in the present case that amyloid deposition is usually extensive involving nerve bundles and ganglion cells as well as the epineural and perineural vessels[5 6 15 18 19] and it is now believed that the neuropathy is mainly due to direct compression of neural structures by the amyloid material The extensive demyelination of nerves found in the present case is probably a nonspecific response of nerve fibers to amyloid deposits

Postural hypotension is a physical sign which is not frequently looked for unless severe enough to produce symptoms Its presence has been noted in most cases of primary amyloidosis with signs of peripheral polyneuropathy which constituted 13 6 per cent in one series[8] it is possible that mild or moderate degrees of ortho

Table II Anatomical distribution of amyloid and extent of its deposition

Organ involved	Tissue	Vessels
Spleen	+++++	+
Heart	++++	+
Adrenals	++++	+
Kidney	++	++
Lip (ulcer)	++	+
Tongue	+	−
Thyroid	+	+
Lung	+	+
Seminal vesicles	±	++
Prostate	±	++
Pancreas	+	−
Liver	−	++
Rectum	−	±
Spinal cord	−	−

Table III Amyloid distribution in left sympathetic chain

Site	Amount
Inferior cervical ganglion	+
Upper thoracic chain	++
Midthoracic ganglion	+++
Splanchnic nerve	+
Lower thoracic chain	+
Upper lumbar ganglion and chain	+
Lumbar ganglion	+

Table IV Amyloid distribution in the peripheral nervous system

	Nerve	Vessels	
		Epineural	Perineural
Lumbar nerve root	+++	+	+++
Sacral nerve root	+++	+	+++
Left median nerve	±	−	+
Cervical posterior root ganglion	++	NA	NA
Right and left median popliteal nerve	+	−	++

normal filling pressure suggesting myocardial failure On standing there was no increase in the peripheral resistance and the arterial pressure fell while the heart rate remained constant There was a slight fall in the cardiac output presumably due to a decrease in venous return During Valsalva's maneuver the patient achieved an increase in the intrathoracic pressure of approximately 30 mm Hg There was no increase in the heart rate during the procedure and no reflex bradycardia or over shoot of the arterial pressure after its termination

The sum total of these findings was taken as evidence of central and peripheral cardiovascular denervation with some degree of myocardial involvement

Autopsy findings

Macroscopic findings There was extensive edema of the legs and sacrum and a large necrotic ulcer at the mucocutaneous junction of the lower lip Both pleural sacs contained serous effusions (right 500 ml left 520 ml) The heart was enlarged and weighed 480 grams The coronary arteries showed a severe degree of stenosing atheroma The myocardium was pale and abnormally firm In the lungs there was some degree of puckering and fibrosis at the left apex and four small pulmonary infarcts in the left lung estimated to be between seven and ten days old with organizing thrombi in the corresponding branches of the pulmonary arteries The peritoneal sac contained 1 200 ml of clear yellowish fluid The liver was firm in consistency and weighed 1 520 grams The gallbladder contained several small mixed stones The spleen was slightly enlarged and weighed 280 grams Its outstanding features were its extreme firmness and its homogenous waxy appearance on cut section The kidneys did not show any macroscopic abnormality and the total kidney mass was 310 grams

Microscopic findings There was widespread deposition of amyloid material in almost all organs the only exceptions being the brain spinal cord and pituitary gland The anatomical distribution and extent of deposition in the different organs is shown in Table II The thoracic and lumbar segments of both sympathetic chains were examined with as many of the branches as possible Extensive amyloid deposition was found throughout the sympathetic ganglia and nerves (Table III and Fig 3) All the peripheral nerves examined showed involvement by amyloid (Fig 4) and the findings are summarized in Table IV The amyloid was deposited both within the nerve bundles and also in the interfascicular (epineural) and intrafascicular (perineural) vessel The nerves showed extensive demyelination Amyloid was also found in the small blood vessel and tissues at the base of the lip ulcer The amyloid substance was identified by the different staining reactions and was examined by ordinary and electron microscopy

Discussion

A review of previous reports of cases of primary amyloidosis reveals that when autonomic manifestations were present there were usually associated signs of peripheral polyneuropathy the autonomic manifestations consisted in most cases of gastrointestinal symptoms impotence or postural hypotension[1,3,9] In a review of


Fig 3 Part of a thoracic sympathetic ganglion with an efferent branch showing infiltration with amyloid (Hematoxylin and eosin × 480)


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154 published cases[8] diarrhea was present in 15 per cent and neurological involvement in 13 6 per cent.

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Postural hypotension is a physical sign which is not frequently looked for unless severe enough to produce symptoms Its presence has been noted in most cases of primary amyloidosis with signs of peripheral polyneuropathy which constituted 13 6 per cent in one series[8] it is possible that mild or moderate degrees of ortho

static hypotension are missed and this sign may be present in a much higher percentage of cases of primary amyloidosis even in the absence of other neurological signs, as in the present case On the basis of this and other reported cases we suggest that this physical sign should be especially looked for in any patient suffering from an obscure neuropathy or the nephrotic syndrome, or suspected to be suffering from amyloid disease, if other more obvious causes of orthostatic hypotension such as diabetes mellitus, neurosyphilis, and hypovolemia are excluded the presence of significant postural hypotension in those cases should raise a strong suspicion of amyloid disease

Summary

A patient with primary amyloidosis who developed severe postural hypotension during the course of the nephrotic syndrome is described hemodynamic studies demonstrated that this was due to autonomic dysfunction and revealed evidence of central and peripheral cardiovascular denervation Pathological examination showed extensive infiltration of sympathetic ganglia and nerves with amyloid material Postural hypotension was the only clinical evidence of neurological involvement in the absence of other manifestations of autonomic disturbance or signs of peripheral neuropathy

We wish to express our thanks to Prof D A K Black for his permission to report this case and to Miss J Barrett for her secretarial help

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Clinical pathologic conference

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Case report

DR. ROBERT N SCHNITZLER A T a 51 year-old garage worker was admitted to Strong Memorial Hospital for the first time in December 1967 with a six month history of increasing fatigue cough exertional and nocturnal dyspnea and orthopnea. Six weeks prior to the admission he had been seen at his local hospital and a digitalis preparation and diuretics were begun. Despite a weight loss of ten pounds he developed ankle edema in addition to his other symptoms. There was no history of hypertension, thrombophlebitis or rheumatic fever

Past history was pertinent in that two years prior to admission his physical examination had been negative. He was known to drink moderately and had smoked two to three packs of cigarettes daily for many years.

On physical examination his blood pressure was 110/70 pulse rate was 96 beats per minute and respirations were 18 per minute The jugular venous pressure measured 4 cm. above the sternal angle and a prominent V wave was observed Dullness and decreased breath sounds were present at the base of the left lung The heart was markedly enlarged and the cardiac impulses suggested biventricular hypertrophy The second sound was widely split and did not move with respiration Pulmonary valve closure was markedly increased A third heart sound was audible at the midclavicular line in the sixth intercostal space A Grade 3/6 holosystolic murmur was heard at the left sternal border and at the apex. The liver was felt 4 cm below the right costal margin and was tender to palpation There was no clubbing of the fingers. Two-plus ankle edema was present.

The laboratory findings included a hematocrit of 40 per cent, a white blood count of 12 600 with 4 per cent polymorphonuclear cells 1 per cent bands 22 per cent lymphocytes 2 per cent monocytes, and 1 per cent basophil The peripheral blood smear was normal Corrected sedimentation rate was 22 mm per hour Urinalysis was negative Blood urea nitrogen glucose serum electrolytes alkaline phosphatase bilirubin uric acid creatinine cholesterol and glutamic oxalacetic transaminase were all within normal limits. Electrocardiographic (ECG) changes included some decrease in QRS voltage and T wave inversion in Leads I aV$_L$ and V$_6$ (Fig 1) Marked cardiomegaly with left atrial enlargement was demonstrated on roentgenography of the chest (Fig 2) In addition a left pleural effusion was present and the lungs appeared congested Kerley B lines were seen.

Because the clinical diagnosis was uncertain cardiac catheterization was performed The results are summarized in Table I On angiography a small left atrium was demonstrated A mass was found compressing the chambers medially and inferiorly no drainage could be demonstrated from the pulmonary veins of the left lower lobe of the lung A filling defect also was noted partially occluding the pulmonary vein of the left upper lobe. Compression of the right pulmonary artery and displacement of the left pulmonary artery by a mediastinal mass were also demonstrated These findings will be discussed in further detail

Other laboratory data included a normal serum protein electrophoresis six negative blood cultures and Class I cells by sputum cytology The patient improved over the next several days and was discharged with instructions to take digoxin. He had refused to undergo further studies

In the ensuing two months the patient did not improve He lost an additional six pounds and developed anorexia increasing dyspnea and pain in the midscapular region. He was hospitalized elsewhere for one week and was successfully treated for a right lower lobe pneumonia He was readmitted to Strong Memorial Hospital in February 1968

On examination he appeared cachectic and

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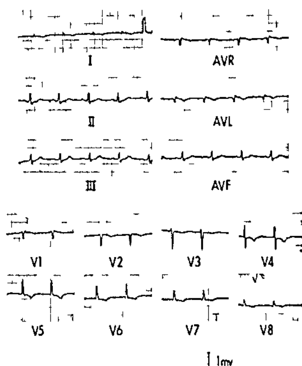


Fig. 1. Initial electrocardiogram taken in December 1967 showing normal sinus rhythm, some decrease in QRS voltage, and generalized nonspecific T wave abnormalities.

chronically ill. The blood pressure was 92/70 without paradox, pulse rate was 95 beats per minute, and respirations were 30 per minute and shallow. The jugular venous pressure measured 9 cm. above the sternal angle. A left cervical lymph node was palpable. Dullness, decreased breath sounds, and râles were present at both lung bases. The cardiac findings were similar to those described in the first admission except for further cardiomegaly. The liver was palpable 4 cm. below the right costal margin and 2+ ankle edema was present.

The hematocrit was 38 per cent, white blood count was 19,100 with a normal differential, and no abnormalities of the peripheral blood smear were seen. Urinalysis was negative. Prothrombin time was 45 per cent of normal. Blood urea nitrogen, serum electrolytes, total protein, and protein electrophoresis were all normal. In addition, normal values for blood glucose, serum alkaline phosphatase, uric acid, calcium, phosphorus, and glutamic oxalacetic transaminase were obtained.

Further cardiomegaly and bilateral pleural effusions were demonstrated on the roentgenogram of the chest. The ECG showed loss of anterior forces in the horizontal plane in addition to low voltage and T wave inversion in Leads I, aVL, and V_{1-6}. Class I cells were consistently observed on sputum cytological examination.

Diuretic therapy was instituted without significant improvement, and the patient continued to deteriorate. Pericardiocentesis was attempted on the seventh hospital day, but no pericardial fluid was obtained. Lymphoid and histiocytic hyperplasia were reported on the biopsy specimen of a left axillary lymph node.

Table I. Results of cardiac catheterization

Variables		*Values*
Cardiac index (L./min./M.²)		3.23
Heart rate (beat/min.)		75
Stroke index (ml./beat/M.²)		43.4
Pressures (mm. Hg)		
Right atrium		a = 10
		v = 11
		mean = 7
Left atrium		v = 35
		mean = 18
Pulmonary artery		phasic = 58/[illegible]
		mean = 3[illegible]
Systemic artery		phasic = 105/65
		mean = 80

On the twelfth hospital day, the patient's blood pressure fell to 88/70 and his pulse rate increased to 110 beats per minute. Pericardiocentesis was again performed with removal of 100 ml. of bloody pericardial fluid. The specific gravity of the fluid was 1.014; its content was total protein 2.7 Gm. per cent. There were 2,375 white cells of which 84 per cent were lymphocytes. Cultures for bacteria and fungi were negative. However, white blood count was persistently elevated. On the nineteenth hospital day, the patient's blood pressure fell further to 76/50, his pulse rate rose to 128 beats per minute, and his respirations were 40. The jugular venous pressure rose markedly but fell during inspiration. The ECG and roentgenogram of the chest remained unchanged. On the twentieth hospital day, the patient died.

Discussion

DR. JULES COHEN: This was a 51-year-old man who developed symptoms of rapidly progressive biventricular cardiac failure, who was poorly responsive to the usual modes of therapy. His physical examination had been normal a year and a half prior to the onset of his symptoms and he was dead within eight months after the disability began. Signs of atrioventricular valve incompetence were present on examination and at cardiac catheterization. At angiography a mediastinal mass lesion was demonstrated. This sequence of events, and the clinical findings were perfectly compatible with a primary mediastinal malignancy involving the heart.

We should try to examine the following questions raised by this case: (1) How might the mass lesion have been responsible for the clinical picture? In particular, what, if any, was the relationship between the mass lesion and the A-V valve incompe-

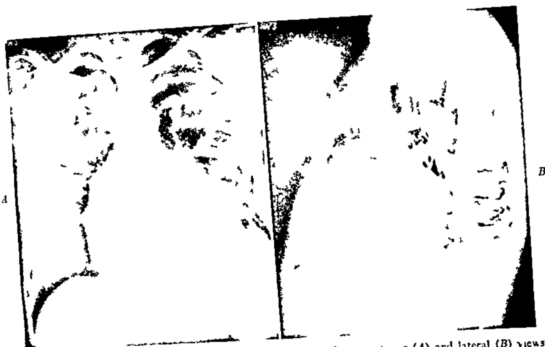


Fig. 2. *A* and *B*. Initial chest roentgenograms December 1967. Posteroanterior (*A*) and lateral (*B*) views. The films show the massively enlarged cardiac silhouette with its irregular outlines, the obscuration of the right hilum, posterior deviation of the esophagus, the left pleural effusion, and evidence of pulmonary venous hypertension.

tence? (2) Was the lesion a primary pericardial or a myocardial neoplasm?

Let us consider first the pathophysiology of the patient's symptoms. His cough, a common symptom in patients with mediastinal tumor, may have resulted from direct local irritation. On the other hand, it may have been the result of left atrial hypertension. The associated pulmonary venous hypertension may have led not only to interstitial pulmonary edema but also to edema of the bronchial mucosa and to conditions conducive to the establishment of bronchitis. These disturbances, coupled with pleural effusion, very likely resulted in his exertional and nocturnal dyspnea and in his orthopnea.

This patient's elevated left atrial pressure was, I believe, largely due to mitral valve incompetence. A sizable V wave was present in the left atrial pressure tracing and the nadir of the rapid y descent reached 0 to 7 mm. Hg (Fig. 3). This suggests that there was little mitral obstruction and that left ventricular diastolic pressure probably was not substantially elevated. Therefore the patient probably did not have significant intrinsic left ventricular dysfunction. Taken together with the substantial inequality in the atrial pressures, this fact makes it unlikely that pericardial restriction played the dominant role in the raised cardiac filling pressures at this point.

One element in the picture suggests another possible basis for raised pulmonary venous pressures, and that is localized pulmonary venous obstruction due to the mediastinal mass lesion itself. Could Dr. Lipchik please review the films and, in particular, tell us whether there was preponderant pulmonary congestion or edema in one lung or the other? If this is the case, do the findings correlate angiographically with the site of pulmonary venous obstruction?

DR. ELLIOT O. LIPCHIK. The first series of films (Fig. 2), taken on December 7, 1967, with barium swallow and oblique views, show a massively enlarged heart shadow with irregular outlines, particularly on the right and with the right hilum obscured (hilum overlay sign).[1] The barium-filled esophagus is displaced posteriorly by this large heart and by mediastinal shadow. There is a massive pleural effusion on the left side only, which depressed the dia

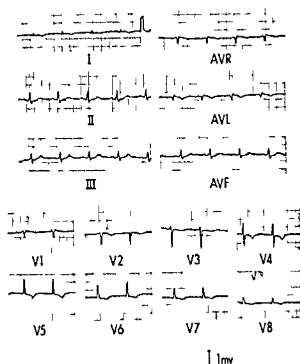


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Systemic artery	phasic =	105/65
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Fig. 5 A and B Pulmonary angiogram done in December 1967 Anteroposterior view (A) and lateral view (B) See text for details

In summary there is a large mediastinal mass intricately involved with the cardiac silhouette displacing and compromising the left atrium and ventricle as well as displacing the esophagus and left pulmonary arteries backward with moderate narrowing and encasement of the right pulmonary artery and with a massive and persistent left pleural effusion There is a filling defect seen in the pulmonary vein draining the left upper lobe with the suggestion of occlusion of the veins from the left lower lobe

DR. JULES COHEN The anatomic evidence thus suggests that pulmonary venous occlusion or obstruction may have accounted in part for this patient s respiratory symptoms as it may in other patients with mediastinal tumor On the other hand in this case the pulmonary artery diastolic pressure was equal to the left atrial pressure Therefore the catheterization data also indicate that the patient had little pulmonary vascular obstruction especially considering the *normal* total pulmonary blood flow

That being the case it appears unlikely that this obstruction resulted *in increased* resistance to total pulmonary blood flow even if the tumor was obstructing one or more pulmonary veins Localized obstruction could account for the findings described by Dr Lipchik The elevated mean pressure in the main pulmonary artery in this case seems more likely reactive and the result of the elevated left atrial pressure due to mitral incompetence

Clinical evidence of right heart failure was also present and this may have been the result of a combination of the pulmonary hypertension and perhaps of tricuspid incompetence—the latter suggested by the initial examination Alternatively obstruction to caval blood flow (not an uncommon consequence of mediastinal and especially of pericardial tumor) might have been present and might have contributed to systemic fluid retention However the transmission of a right atrial pressure wave to the jugular venous pulse suggests that at least superior vena cava obstruction was not present Finally had the tumor infiltrated the right ventricular myocardium or largely impaired right ventricular filling by virtue of pericardial obliteration the resulting restrictive process might have contributed to right ventricular failure But the form of the right ventricular pressure pulse was not that of pericardial or myocardial restriction

The physiologic findings therefore suggest that the left heart failure here probably was largely related to the demonstrated *mitral incompetence although localized* pulmonary venous obstruction with localized pulmonary edema may also have contributed to the picture The right heart failure may have been more complicated and the result of a combination of reactive pulmonary hypertension tricuspid valve incompetence and possibly though less likely the addition of caval obstruction and/or involvement of the right ventricular

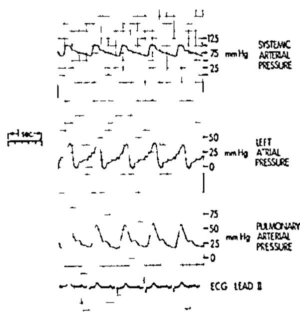


Fig 3 Results of cardiac catheterization December 1967 The systemic arterial pressure was normal but both the pulmonary arterial and left atrial mean pressures were raised and a prominent V wave was present in the left atrial pressure pulse The pulmonary artery diastolic pressure and left atrial mean pressure were nearly equal suggesting that significant generalized pulmonary venous obstruction was not present.



Fig 4 Chest roentgenogram taken in February, 1968 See text for details

phragm and impinges upon the superior aspect of the air filled gastric fundus On the Bucky overpenetrated film of the chest, the pleural effusion can be seen collecting alongside the mediastinum and obliterating the paravertebral and aortic densities There is no evidence of calcification, air fluid levels or significant atelectasis The upper lobe veins are dilated indicating pulmonary venous hypertension

The chest film two and a half months later (Fig 4) shows further enlargement of what appears to be a large cardiomediastinal density with complete obliteration of the left cardiac border and increased effusion on the left side The bones do not show any evidence of metastatic disease There are old healed rib fractures on the right. The trachea is midline

Shortly after the first series of chest films, both a pulmonary angiogram and a left cineangiocardiogram were performed with the injection of 40 ml of 75 per cent Hypaque solution into the main pulmonary artery followed by the injection of the same amount of contrast material directly into the left atrium This latter study was performed with a Brockenbrough catheter, passed transseptally from the right to the left atrium Cine films were obtained at 60 frames per second

The pulmonary angiogram (Fig 5) shows marked narrowing of the main right pulmonary artery as it traverses the mediastinum The bifurcation of the right pulmonary artery appears normal with good visualization of the branches of the upper and lower lobes, showing no abnormality There is prolonged holdup of contrast material into the arteries to the lingula and lower lobes These vessels are displaced posteriorly and are somewhat narrowed There is no evidence however of proximal pulmonary occlusions The venous return from the right lung and the left upper lobe is normal

The cine angiocardiogram showed a normal to small left atrium with an extrinsic mass compromising the left atrium medially and from below Reflux into the veins from the right lung showed no abnormality whereas there is a filling defect in the confluent vein from the left upper lobe There was no reflux into the veins of the left lower lobe The left ventricle is normal in size with rather poor contractions, particularly of the lateral aspect The mediastinal density extends for several centimeters beyond the defined lumen of the ventricle out almost to the chest wall



Fig 6 Interlacing bundles of spindle cells with hyperchromatic nuclei and scant cytoplasm form the solid portion of the tumor (Hematoxylin and eosin Original magnification ×280)

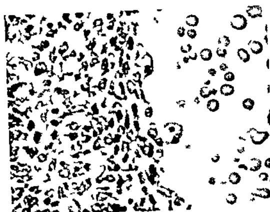


Fig 7 The cystic area are lined by epithelial like cell The cytoplasmic vacuolated inclusions seen in these cells contain mucopolysaccharide Both these and the globules seen within the cyst were stained with periodic acid Schiff and the colloidal iron method (Hematoxylin and eosin Original magnification ×480)

heart muscle in the region of the atrioventricular valve rings thereby contributing to the A V valve incompetence From the angiographic data impingement of the tumor on the left atrium posteriorly inferiorly and superiorly and impingement on the pulmonary arteries is to be expected Speaking strictly statistically either primary mesothelioma or sarcoma of the pericardium would be most likely[5 6]

Pathologic findings

DR ERIC A SCHENK When the thorax was opened a 20 by 17 by 16 cm mass which compressed both lungs and pushed them into the upper portion of the thoracic cavities was found in the mediastinum The pleural surfaces were smooth except for a few fibrous adhesions between the visceral pleura and the generally smooth surface of the tumor mass The right pleural cavity contained 1 500 ml and the left cavity contained 2 ,00 ml of thin red tinged slightly cloudy fluid The excised mediastinal mass weighed ? 870 Gm and contained the heart the ascending aorta and arch the pulmonary artery and veins the trachea and its bifurcation and the left and right main bronchi and esophagus

The pericardial sac was obliterated and the tumor extended to the surface of the heart Sections through the tumor showed variable structural features Both cystic and solid areas were present The cysts were single and multiloculated some were filled with clear yellow fluid and others with grayish yellow friable or gelatinous material The solid areas ranged from soft and yellow to firm and gray Although all of the contents in the anterior and posterior mediastinum were surrounded by this tumor there appeared to be no grossly apparent extension into these structures

The heart could not be dissected from the tumor mass which completely surrounded and encased it. Both left and right ventricles were moderately dilated with some flattening of the trabeculae carneae In contrast both atria appeared compressed and small There was also compression of the pulmonary artery and veins

Microscopic examination showed most of the tumor to be composed of spindle shaped cells arranged in a regular interlacing pattern The spindle cells were generally small with oval or irregular hyperchromatic nuclei and a scant amount of cytoplasm (Fig 6) Prominent nucleoli and mitoses were infrequent Special stains for reticulum and collagen showed these elements associated only with blood vessels within the tumor The systic areas were irregularly lined by epithelial like cells with abundant cytoplasm which contained periodic acid Schiff (PAS) staining material The cystic spaces were filled with desquamated cells and globules which stained with both the periodic acid Schiff and colloidal iron methods for mucopolysaccharides (Fig 7) Spindle shaped tumor cells infiltrated the epicardium as well as the adventitia of the large arteries and veins in the superior

myocardium with tumor. There was no clinical or hemodynamic evidence of obstruction to outflow from either ventricle. However, patients with tumor encircling and obstructing either the pulmonary artery or the aorta or both have been described, and this possibility should be kept in mind in the evaluation of such patients. In any case, it seems here that much of the clinical picture was secondary to the substantial A-V valve incompetence that accompanied the basic pathology.

What are the possible mechanisms of A-V valve incompetence in patients like this? Intracardiac tumor may mechanically interfere with valve leaflet movement. I don't think this is the case here, because usually such patients demonstrate obstruction to flow as well, and there was no clinical or hemodynamic evidence of either mitral or tricuspid obstruction. Intraventricular tumor may involve the supporting structures of the valve and impair valve closure, but angiographically the tumor in this case did not appear to involve the left ventricular cavity. Actual invasion of the myocardium may produce enough ventricular dysfunction to dilate the ventricle and the A-V valve ring, thereby producing functional A-V valve incompetence. As we discussed earlier, the catheterization and angiographic data do not support such an explanation for the mitral incompetence, but this remains a possible explanation of the tricuspid incompetence. Endocarditis might supervene in a patient with a mediastinal malignancy and produce A-V valve lesions, but there is really nothing to suggest this complication in this patient. Conceivably, pericardial tumor especially might produce coronary obstruction and lead either to left ventricular or papillary muscle dysfunction and mitral incompetence on this basis.[2] It also has been suggested that tumor invasion of the pericardium and the heart may sufficiently impair cardiac motion or distort the position of the heart and the A-V valve rings so that valve closure is impaired. While such a hypothesis is by no means proved, this also seems a reasonable explanation of the A-V valve incompetence in this case. Actual destructive invasion of the tumor into the valve substance itself is a possibility, in view of the impingement of the tumor on the atrial shadow inferiorly at angiography.

I want to consider the last point now, and present the arguments for this being a primary cardiac neoplasm rather than a primary tumor, of the lung for example, with spread to the heart. I also want to examine the basis for considering this a lesion of the pericardium rather than primarily of the myocardium or endocardium.

I think one would have expected other clinical evidence of a primary lung lesion or of a lymphoproliferative disorder, or of some other more distant malignancy, if the mediastinal mass lesion had been secondary to such a process. Furthermore, unless the malignancy had produced a sizable pericardial effusion with tamponade, which did not seem to be the case here, one would not have expected the cardiac disability to have so dominated the clinical picture, or to have been so rapidly progressive. In addition, the radiographic appearance of the cardiac silhouette is suggestive of a primary cardiac or pericardial lesion.

Finally, the clinical and, in particular, the radiographic findings suggest that we're dealing with a primary pericardial lesion rather than with a myocardial or endocardial lesion. Although it is somewhat surprising that the tumor did not produce more of a restrictive process, the mass seems external to the left atrium and ventricle angiographically. It has produced a hemorrhagic pericardial effusion. In contrast, there is no evidence of obstruction to blood flow within the heart, which one might expect of an endocardial mass lesion.[3] Neither clear ventricular dysfunction nor conduction disturbances were present, and one might have expected these in a tumor which had significant myocardial spread.[4] One would certainly have expected either obstruction to intracardiac flow or ventricular dysfunction from an endocardial or myocardial tumor which had produced this degree of cardiac enlargement and of compression external to the heart itself. I suppose it's possible that an angiosarcoma arising from one of the pulmonary veins could have produced the picture, but here again I would have expected to see an intracavitary lesion extending into the left atrium as well.

To conclude then, I think the evidence favors an extensive primary pericardial neoplasm. We may also hear from Dr. Schenk that the tumor had invaded the

The jugular pulse in pericardial constriction Its differentiation from that of cardiomyopathy

*Charles P Lisa M D **
*Gary Hood M D ***
Morton E Tavel M D
Indianapolis Ind

Differentiation of cardiomyopathies especially of the restrictive type from constrictive pericarditis is often a most difficult clinical problem Symptoms reflecting restriction may dominate each heart size may be normal or slightly enlarged in both bedside examination of the external jugular pulse may reveal distended veins with a rapid Y descent Cardiac catheterization frequently does not resolve the issue and often thoracotomy with pericardial or myocardial biopsy is required for a definitive diagnosis

Analysis of the jugular pulse recording of the phonocardiogram has proved to be quite useful in clinical assessment of these difficult patients In this study we have attempted to evaluate critically the diagnostic worth of phonocardiography with jugular pulse analysis in this difficult distinction and to compare its diagnostic value to that of cardiac catheterization

Materials and methods

Phonocardiograms with external jugular pulse recordings from 12 patients with proven constrictive pericarditis and 12 patients with cardiomyopathies were analyzed all showed the square root configuration in the jugular pulse recording Phonocardiograms were obtained from 1? normal subjects who served as controls

Indirect jugular pulses were recorded by the method described by Tavel [1] A funnel shaped pick up device with an open end (2 5 cm diameter) was held over the internal jugular vein usually about 1 cm above the clavicle and 1 cm to the right of the sternoclavicular joint between the manubrial and clavicular insertions of the sternocleidomastoid muscle The open end of the funnel was angled downward toward the diaphragm at approximately 4? degrees Tracings were recorded during held expiration in the recumbent position with the head elevated on one pillow The funnel was connected to a piezoelectric microphone (Sanborn No 374) The electrical signals were recorded graphically with an Electronics for Medicine Recorder (Model DR 8) The incoming signals were filtered with a band pass filter set at a range of 0 1

With the technical assistance of Jamie Stewart
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Supported in part by the Herman C Krannert Fund Eli Lilly and Company United States Public Health Service Grants HE-09815-06 HE 6308 HTS-5363 and HE-5749 and the Indiana Heart Association.
Reprint request to Morton E. Tavel, M D Fesler Hall, Room 110 Indiana University Medical Center 1100 W Michigan St. Indianapolis, Ind 46202
*Trainee in Cardiology Department of Medicine Indiana University School of Medicine.
**Formerly Senior Medical Student, Indiana University School of Medicine.

mediastinum, but there was no invasion of the myocardium or walls of the blood vessels Similarly, no extension into the trachea or esophagus was apparent on any of the sections There were no metastases to lymph nodes or other organs Other significant pathologic findings were marked bilateral acute and chronic congestion of the lungs, bilateral atelectasis of the lower lobes of the lung, hepatomegaly (2,200 Gm) and splenomegaly (260 Gm) with chronic congestion, and ascites (1 000 ml)

The localization of this tumor in the pericardial region and its histologic appearance, an admixture of spindle cells and pseudoglandular or cystic elements, indicate that this is a fibro epithelial or mixed type of mesothelioma of the pericardium [7] It is further classified as a benign or nonaggressive mesothelioma because it remained confined to the pericardial region and even in this area its infiltrating proclivity was minimal

The number of mesotheliomas of the pericardium which have been reported and reviewed is still small[7, 9] and there is controversy about certain aspects of these tumors It is not clear whether some of the more malignant varieties with extra pericardial spread arose from pericardium or from some other site such as the pleura The pure spindle cell varieties have not been uniformly accepted as mesothelial in origin and are referred to as fibrosarcomas in some reports [10] Mesotheliomas arising from the pleura and peritoneum often secrete mucoid material containing hyaluronic acid, which may be present in the effusions produced by these tumors [11, 12] One previous attempt to demonstrate polysaccharide in tissue sections from a benign mixed mesothelioma of the pericardium was unsuccessful [13] The presence of cells and secretory material which stain with the periodic acid Schiff and with the colloidal iron method in our case indicates that the pericardial mesotheliomas are capable of producing an acidic mucopolysaccharide, although its production like the histologic pattern may be more variable than that seen with pleural and peritoneal mesotheliomas

The dysfunction resulting from the presence of this tumor must have been due to extrinsic compression of the heart and blood vessels at the base of the heart The atria and pulmonary artery and veins were apparently most obviously compressed There is no morphologic explanation for the proposed mitral valve incompetence The circumference of the valve was of average size, and there was only a moderate degree of left ventricular dilatation The encasing tumor mass may have ' fixed ' the size and shape of the heart so as to produce valvular insufficiency

FINAL ANATOMIC DIAGNOSIS *Benign mixed (fibro epithelial) mesothelioma of the pericardium,* blood tinged pleural effusions (1 500 ml right, 2,700 ml left), atelectasis of both lower lobes of lungs acute and chronic congestion of lungs, congestive hepato splenomegaly, ascites

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Table III Summary of mean values

Patient group	A_2V	PA	PA_d	$\overline{PA}$	RV	RV_d	$\overline{RA}$	$RV - \overline{RA}$
Normal ± S.D	0 10 ± 0 027	—	—	—	—	—	—	—
Cardiomyopathy ± S.D	0 07 ± 0 043	57 ± 16 1	29 ± 9 9	38 ± 9 6	55 ± 13 8	13 ± 5 1	14 ± 6 1	43 ± 11 1
Constrictive pericarditis ± S.D	0 00 ± 0 065	34 ± 8 4	18 ± 6 9	27 ± 7 3	35 ± 9 3	15 ± 8 5	15 ± 7 5	20 ± 5 7
P value	<0 01	<0 05	N.S.	N.S.	<0 01	N.S.	N.S.	< 001

Abbreviations S D = standard deviations N S. = not significant Other abbreviations as in Table I

proven diagnosis diagnosis was made on the basis of the entire clinical picture including electrocardiogram chest x ray fluoroscopy catheterization data and clinical course None of the patients manifested evidence of significant tricuspid insufficiency

Results

Data from phonocardiograms and cardiac catheterization are presented in Tables I and II The mean pressures for the pulmonary artery right ventricle and right atrium and the difference between right ventricular systolic and right atrial mean pressures are listed in Table III They show elevation of all pressures in both groups however the right ventricular systolic pressure is elevated to a greater degree in the cardiomyopathy group than in the constrictive group (p <0 01) Further there is a striking difference (p <0 001) between the differences of right ventricular systolic and right atrial mean pressures in the two groups The mean A_2V interval (Table III) for the cardiomyopathy group is 0 07 second and for the constrictive pericarditis group 0 00 second this difference is also significant (p <0 01) Fig 1 illustrates the distribution of the A_2V intervals in the normals and both patient groups It can be seen that in all normal controls the A_2V interval exceeded 0 03 second The cardiomyopathy group was similar with only 3 of 12 patients having an A_2V interval less than 0 03 second with the remainder exceeding this value Conversely 9 of 12 in the constrictive pericarditis group showed an A_2V less than 0 03 second while in only 3 patients the A V interval exceeded 0 03 second Figs 2 and 3 show typical examples of each group

Discussion

There has been an abundance of literature pointing out the similarities and differences in clinical and hemodynamic manifestations of constrictive pericarditis and cardiomyopathies[2-4] While the contour of the right atrial pressure pulse seen in constrictive pericarditis was once felt to be pathognomonic for this entity[7] it is now well established that disease entities which restrict ventricular filling by involving the endocardium or myocardium[2-4] may produce an identical pattern

Phonocardiography may provide a useful and easily performed adjunct in this difficult clinical problem While the basic contour of the jugular pulse wave in cardiomyopathy and constrictive pericarditis may be identical the earlier appearance of the V wave in constriction usually distinguishes the two groups As can be seen in Fig 1 an A_2V interval of less than 0 03 second is strong evidence for constrictive pericarditis an A_2V exceeding 0 03 favors cardiomyopathy

While the precise mechanisms underlying these differences in timing are subject to speculation we feel that correlation with catheterization data (summarized in Table III) provides an explanation In the cardiomyopathy group there is striking elevation of right ventricular systolic pressure with only a slight increase in diastolic pressure and in right atrial pressure As a result the right ventricular pressure must fall a considerable distance before it drops below right atrial pressure and allows the tricuspid valve to open The isovolumic relaxation period of the right ventricle is therefore relatively long and this is reflected in the long interval from the second sound to the V wave peak On the other

Table I. A_2V intervals and cardiac catheterization data of cardiomyopathy patients

Patient	A_2V	PA_s	PA_d	$\overline{PA}$	RV	RV_d	$\overline{RA}$	$RV-\overline{RA}$
E L	0 04	88	45	50	—	—	23	—
G L	0 00	30	14	19	30	9	8	22
C H	0 09	55	36	41	55	19	16	39
J L	0 11	—	—	—	—	—	—	—
S M	0 14	52	21	33	65	16	15	50
E S	0 01	—	—	—	—	—	—	—
I U	0 10	70	32	43	70	17	12	58
T W	0 14	56	28	39	56	15	15	41
K W	0 14	57	23	39	57	9	8	49
S S	0 09	53	32	39	53	4	5	48
A P	−0 08	75	43	53	75	20	24	51
G R	0 09	38	17	25	36	10	9	27
Mean	0 07	59	29	38	55	13	14	43

Abbreviations A_2V = interval from aortic closure to V wave peak (sec) PA_s = pulmonary artery systolic pressure PA_d = pulmonary artery diastolic pressure $\overline{PA}$ = mean pulmonary artery pressure RV = right ventricular systolic pressure RV_d = right ventricular diastolic pressure $\overline{RA}$ = right atrial mean pressure $RV - \overline{RA}$ = difference between right ventricular systole and right atrial mean pressures (All pressures in mm Hg)

Table II. A_2V intervals and cardiac catheterization data of constrictive pericarditis patients

Patient	A_2V	PA_s	PA_d	$\overline{PA}$	RV	RV_d	$\overline{RA}$	$RV-\overline{RA}$
W W	−0 09	—	—	—	—	—	—	—
J S	0 06	27	10	16	27	6	8	19
D I	−0 02	31	18	24	32	15	14	18
D B	0 00	37	19	28	37	18	16	21
J S	−0 02	21	10	17	21	9	10	11
C S	0 11	36	18	25	36	10	13	23
B J	−0 03	—	—	—	—	—	—	—
M M	−0 04	42	22	32	45	20	16	29
H W	0 02	—	—	—	—	—	—	—
P W	0 04	45	30	36	47	31	31	16
A W	−0 09	—	—	—	—	—	—	—
L C	0 02	—	—	—	—	—	—	—
Mean	0 00	34	18	27	35	15	15	20

Abbreviations as in Table I

to 20 cycles per second (c p s) Recording speed was 100 mm per second and time lines were set at 0 1 second intervals

The jugular pulse recording was analyzed and the interval from aortic closure to the peak of the V wave (A_2V) was determined A_2 rather than P_2 was used as a reference point because it is more easily identified in the phonocardiogram Five complexes were analyzed and average values were used

Right and retrograde left heart catheterization was performed on 10 of 12 patients with cardiomyopathies and 7 of 12 patients with constrictive pericarditis Pressures were recorded in all heart chambers, the pulmonary artery and a systemic artery dye curves were done to exclude a shunt Definitive diagnosis was made in two cardiomyopathy patients at autopsy (subendocardial fibroelastosis and amyloid) and an additional patient had a histologically normal pericardium at surgery Five patients with constrictive pericarditis had a definitive histologic diagnosis made by biopsy or necropsy study In the remaining patients i e those without a histologically

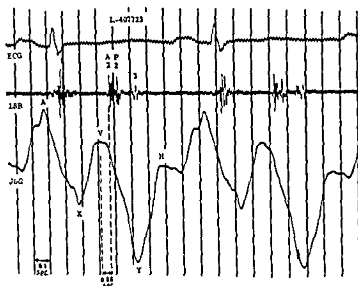


Fig. 3 Example of findings typical for constrictive pericarditis $A_2V = -0.06$ sec

to our total group of patients the diagnosis would have been correct in 18 out of 24 patients. Tricuspid insufficiency with a pronounced and early V wave might potentially simulate pericardial constriction. The presence of the typical jugular contour and associated clinical findings of tricuspid disease however should allow one to distinguish it from pericardial constriction.

Phonocardiography with jugular pulse analysis provides a simple inexpensive noninvasive and reasonably accurate adjunct in the differentiation between cardiomyopathy and constrictive pericarditis. When correlated with the clinical presentation and other laboratory data it is quite helpful in this difficult clinical problem. When one further analyzes other components of the routine phonocardiogram especially the characteristic pattern of retraction seen in the apexcardiogram in constrictive pericarditis and the morphology of the Y descent in the jugular pulse recording[8] phonocardiography may even prove decisive in this difficult clinical problem.

Summary

Study of the indirect jugular pulse has potential value in differentiation of cardiomyopathies from constrictive pericarditis often a difficult clinical problem. Twelve patients with constrictive pericarditis were compared with 12 patients with cardiomyopathy and 15 normal subjects. The interval between the aortic second sound and the jugular V wave peak (A_2V) was determined for each case. Nine of 12 patients with cardiomyopathy and all 15 normal subjects had an A_2V greater than 0.03 second while in 9 of 12 cases with constrictive pericarditis A_2V was less than 0.03 second. Thus using A_2V alone the distinction between cardiomyopathy and constrictive pericarditis could be made in 18 of our 24 patients. A_2V reflects the isovolumic relaxation time of the right ventricle. This is shortened in constrictive pericarditis because of a high right atrial pressure and relatively normal right ventricular pressure. Study of the jugular pulse in this manner provides a safe inexpensive and noninvasive adjunct in diagnosing constrictive pericarditis.

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A_2V INTERVALS FOR NORMALS, CARDIOMYOPATHIES AND CONSTRICTIVE PERICARDITIS

Fig. 1. Distribution of the A_2V intervals within the various groups.

Fig. 2. Example of findings typical for cardiomyopathy. A_2V = 0.11 sec.

hand in constrictive pericarditis relatively normal right ventricular systolic pressure persists with an elevated diastolic pressure and right atrial pressure. Hence, isovolumetric relaxation of the right ventricle is short, producing a short or even negative A_2V interval.

Consideration of some individual patients in our study lends support to this hypothesis. Patients J. S. and C. S. (constrictive group, Table II) each had a right ventricular systolic to diastolic pressure ratio of greater than 3 to 1, which is unusual in constrictive pericarditis; in addition each had a relatively low mean right atrial pressure. The A_2V intervals for these patients were respectively 0.06 and 0.11 second, more in keeping with cardiomyopathy. All other catheterized patients in the constrictive pericarditis group had right ventricular systolic-to-diastolic pressure ratios less than 3:1. Patient A. P. (cardiomyopathy group, Table I) had an A_2V interval measuring −0.08 second. Note that his right atrial pressure was the highest recorded in this group.

Using the criteria outlined above, namely that an A_2V interval less than 0.03 second favors constrictive pericarditis while a value exceeding this is consistent with cardiomyopathy, a high degree of diagnostic accuracy is attained. Applying these criteria

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Julian Frieden

The medical treatment of angina pectoris IV Nitroglycerin as an antianginal drug

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Nitroglycerin is considered by most physicians to be effective in the treatment of angina pectoris However Master Jaffe and Dack[1] stated in 1939 that in 89 patients with angina pectoris due to coronary artery disease sublingual nitroglycerin was not better than a placebo in the treatment of angina pectoris † Fisch and DeGraff[2] demonstrated in a double blind study that nitroglycerin administered sublingually to 9 patients with angina pectoris due to coronary artery disease at the onset of exercise induced angina was not significantly better than placebo in shortening the duration of the anginal attack Sandler Ilahi and Lawson[3] also showed in a double blind study that nitroglycerin administered sublingually to 15 patients with angina pectoris due to coronary artery disease in doses of either 0 25 mg 0 50 mg or 1 0 mg at the onset of an episode of exercise induced angina did not cause any significant change in the duration of the anginal attack or in the duration of ischemic ST segment depression in the electrocardiogram (ECG) in comparison with placebo

Riseman and Brown[4] reported that the duration of exercise induced angina pectoris without medication was less than 1 minute in 18 of their 37 patients (49 per cent) with angina pectoris due to coronary artery disease In 61 per cent of these 18 patients sublingual nitroglycerin did not alter the duration of anginal pain In 22 per cent of these 18 patients sublingual nitroglycerin decreased the anginal attack by about one third In 17 per cent of these 18 patients sublingual nitroglycerin increased the anginal episode by about one third These investigators[4] showed that the duration of exercise induced angina pectoris without medication lasted from 1 to 2 minutes in 16 of their 37 patients (43 per cent) In 62 per cent of these 16 patients sublingual nitroglycerin shortened the anginal episode In 38 per cent of these 16 patients sublingual nitroglycerin did not alter the duration of the anginal pain Riseman and Brown[4] demonstrated that the duration of exercise induced angina without medication lasted from 2 to 3 5 minutes in 3 of their 37 patients (8 per cent) Sublingual nitroglycerin significantly shortened the duration of the anginal episode in all 3 of

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†Personal communication from Dr Master who now feels that sublingual nitroglycerin is of value in the treatment of angina pectoris.

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minutes prior to treadmill exercise caused an average increase of 125 per cent over the control value in the amount of exercise performed before the appearance of angina and an average increase of 121 per cent over the control value in the amount of exercise performed before the onset of ischemic ST segment depression Fourteen of their 16 patients (88 per cent) exhibited more than 50 per cent increase in exercise tolerance over the control value before the onset of angina pectoris Goldstein and his associates[8] demonstrated that nitroglycerin administered sublingually to 8 patients with angina pectoris due to coronary artery disease 3 minutes before upright bicycle ergometer exercise caused a significant increase in exercise capacity and a significant delay in the onset of ischemic ECG changes in comparison with placebo

Detry and Bruce[9] reported that 0 4 mg of nitroglycerin administered sublingually to 39 patients with angina pectoris due to coronary artery disease at the onset of treadmill exercise caused a significant increase in the maximal heart rate a significant increase in the product of systolic blood pressure and heart rate and significantly less ischemic ST segment depression during and after exercise Twelve of these 39 patients (38 per cent) were also symptomatically limited by dyspnea and fatigue rather than by chest pain Parker West and DiGiorgi[10] found that 0 5 mg of chewable nitroglycerin administered to 7 patients with angina pectoris due to coronary artery disease approximately 10 minutes prior to supine leg exercise caused only 2 of these 7 patients to experience angina and their angina was less severe than that experienced during the control period The hemodynamic response to this exercise following prophylactic nitroglycerin was also normal in these 7 patients

However it should also be pointed out that in a double blind study Fisch and DeGraff[2] showed that nitroglycerin administered sublingually to 9 patients with angina pectoris due to coronary artery disease 10 minutes before upright bicycle ergometer exercise did not improve the exercise tolerance in comparison with placebo

Needleman[11] reported that high doses of nitroglycerin administered 3 times a day to rats produced tolerance to the blood pressure response of nitroglycerin However Modell[12] pointed out that the development of tolerance to nitroglycerin from even unusually frequent clinical use was not common Wei[13] reported in a double blind study that administration of sublingual isosorbide dinitrate for 4 weeks to 17 patients with angina pectoris due to coronary artery disease did not cause any clinical impairment of the effective response of angina pectoris to sublingually administered nitroglycerin

Lange Reid and Bernhard[14] reported that non atheromatous coronary heart disease may develop on withdrawal from marked chronic nitroglycerin exposure These investigators found that 8 of 160 female munitions workers (5 per cent) developed angina pectoris after withdrawal from nitroglycerin exposure for 48 hours Two of these 160 munitions workers (1 per cent) developed prolonged episodes of coronary insufficiency and 3 of these 160 munitions workers (2 per cent) developed myocardial infarction with 1 of these 3 patients dying This death occurred in a previously normal 40 year-old person All but one of these survivors left the chronic exposure to nitroglycerin and improved Their data suggest that some patients with or without coronary artery disease may develop withdrawal symptoms if nitroglycerin or other nitrite preparations are suddenly stopped after regular frequent heavy long term usage

Finally we agree with Modell[12] that oral as opposed to sublingual administration of nitroglycerin is of little clinical value and that none of the nitroglycerin preparations designed for delayed absorption in the gastrointestinal tract have any merit There are also no well controlled studies which show that nitroglycerin administered either orally in an ordinary tablet or in sustained release form or as a skin ointment is effective as an antianginal drug

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these patients. These investigators[4] also found that 0.3 mg. of nitroglycerin administered sublingually was as effective as a 0.6 mg. dose in relieving angina and was less likely to cause headache. A dose of 0.12 mg. of sublingual nitroglycerin was, however, less effective than a 0.3 mg. dose in relieving angina.

Using a standardized interview, Horwitz, Herman, and Gorlin[5] questioned patients who had taken sublingual nitroglycerin for chest pain due to and not due to significant coronary artery disease as documented by coronary angiography. Almost all of their patients had used 0.3 mg. or 0.4 mg. nitroglycerin tablets and virtually all had used more than one tablet at a time. Horwitz, Herman, and Gorlin[5] found that 37 of their 49 patients (76 per cent) with angina pectoris due to significant coronary artery disease reported that their anginal pain was usually or always relieved in less than 3 minutes after administration of sublingual nitroglycerin. Eighteen of these 49 patients (37 per cent) experienced consistent relief of their angina pectoris in less than 1 minute after administration of sublingual nitroglycerin. Eight of these 49 patients (16 per cent) regularly experienced relief of their anginal pain from 4 to 15 minutes, usually about 5 minutes, after administration of sublingual nitroglycerin. Relief of anginal pain in these patients was often incomplete. Four of these 49 patients (8 per cent) reported that nitroglycerin did not affect their chest pain. The patients with angina pectoris due to significant coronary artery disease who had delayed relief or no relief of their anginal pain following sublingual nitroglycerin tended to have more frequent and intense anginal pain, more coronary artery involvement by obstructive lesions, and more hemodynamic or wall motion abnormalities than those patients who experienced relief of their anginal pain within 3 minutes after administration of sublingual nitroglycerin.

Horwitz, Herman and Gorlin[5] also reported that 4 of their 21 patients (19 per cent) with chest pain not due to significant coronary artery disease as documented by coronary angiography experienced relief of their chest pain within 3 minutes after administration of sublingual nitroglycerin. Nine of these 21 patients (43 per cent) experienced relief of their chest pain after more than 3 minutes, usually after 5 minutes or more, following administration of sublingual nitroglycerin. Eight of these 21 patients (38 per cent) reported that sublingual nitroglycerin was never effective in relieving their chest pain.

Our experience is that sublingual nitroglycerin is not necessary for treating a mild episode of angina pectoris. Cessation of exertion with motionless standing causes pooling of blood in the lower extremities and relieves angina. Sublingual nitroglycerin is, however, effective in treating a more severe episode of angina pectoris. We recommend using an initial dose of 0.3 mg which often suffices and is less likely to induce headache or other unpleasant side effects. Patients should be instructed not to take more than 2 to 3 sublingual nitroglycerin tablets over a period of 15 minutes for a prolonged anginal attack. Additional nitroglycerin should not be taken as the patient may be having an acute myocardial infarction.[6] There is also the danger that the systemic hypotension and decreased coronary blood flow induced by sublingual nitroglycerin might also convert an episode of prolonged angina pectoris into a myocardial infarction.

Nitroglycerin, in our experience, is most useful as an antianginal drug when administered sublingually 2 to 3 minutes prior to performing activities or encountering stressful situations in which an anginal attack may be anticipated. Sandler, Ilahi, and Lawson[3] reported in a double blind study that nitroglycerin administered sublingually to 12 patients with angina pectoris due to coronary artery disease in doses of 0.25 mg., 0.50 mg., and 1.0 mg. 3 minutes prior to exercise significantly increased the amount of exercise performed before angina pectoris developed in comparison with placebo. There was no significant difference in the amount of exercise performed between these 3 doses of nitroglycerin. The 0.25 mg. and 0.50 mg. doses, but not the 1.0 mg. dose, also significantly decreased the duration of the anginal attack.

MacAlpin, Alvaro, and Kattus[7] showed that nitroglycerin administered sublingually to 16 patients with angina pectoris due to coronary artery disease in doses ranging from 0.3 mg. to 0.6 mg. 2 to 4

Annotations

On the chemical nature of basophilic (mucoid) degeneration of myocardium

The term basophilic degeneration (BD) of myocardium is applied to the presence of a basophilic, finely granular material in the cytoplasm of isolated myocardial fibers. This condition is also known as mucoid or mucinous degeneration and cardiac mucoid. It was first recognized by Geipel[1] in 1905 and has been the subject of numerous studies. It is primarily a human condition although it has been seen exceptionally in animals. Its etiology is uncertain. The degree of BD found in a heart is mainly related to the age of the individual. There are three diseases however in which BD is usually present to a much greater degree than one would expect from age alone.[2-4] These are (1) Lafora's disease (a familial form of myoclonic epilepsy) (2) hypothyroidism and (3) idiopathic myocardiopathy.

Very little is known of the significance mechanism of formation and chemical composition of BD. In a recent study by the writer[5] BD was found in 88.88 per cent of the 135 hearts examined. Whereas it was never seen in patients who had died in the first decade of life it was found in all individuals after the age of 11 years with only one exception. A definite correlation was found between increasing age and the extent of the degeneration.

BD's reaction was positive to these techniques all known to stain glycogen periodic acid–Schiff Langhans iodine Best's carmine and Gomori's lithium-silver. It also stained with Mowry's colloidal iron and with Alcian blue (the latter when performed at a pH of 2.5). Stains for amyloid DNA RNA elastic tissue calcium and iron were negative. Incubation of the tissue sections with malt diastase for 30 min. (the usual time employed for the removal of glycogen) did not produce any appreciable effect. However prolonged periods of incubation (up to 48 hours) with the same enzyme abolished the periodic acid Schiff (PAS) positivity. If the sections or tissue blocks were pretreated with chloral hydrate or boiled in distilled water 30 min. of diastase was sufficient to completely remove the deposits of BD. Amyloglucosidase (α-1 4-glucan glucohydrolase) and pectinase were the only other enzymes tested which removed the deposits. By electron microscopy BD deposits were seen as sharply circumscribed foci composed mainly of short straight fibrils 60 to 70 Å in width running in a haphazard fashion with no axial periodicity. Scattered among the fibrils were a few round dense granules 150 Å in diameter compatible with glycogen β particles.

BD was isolated from myocardium containing extensive deposits using Pfluger's method[6] hearts without BD were used as controls. The isolated material had a concentration of 0.92 μmoles of polyglucose per gram. It was completely degraded by the combined action of phosphorylase and debranching enzyme. Its infrared spectrum was practically identical to that of a sample of rabbit liver glycogen.

The results we have obtained with this combined histochemical ultrastructural and biochemical approach favor the interpretation that BD is basically composed of a glucose polymer (glucan or polyglucosan). It has many features in common with three other substances that can be found in human tissues (1) corpora amylacea of the central nervous system (2) intraneuronal Lafora's bodies (seen in Lafora's disease) and (3) the deposits of abnormal glycogen present in glycogenosis IV.[6] In all of these substances chemical studies have also indicated the polyglucosan nature of the deposits.

With the support of these observations we postulate that the branched glucan deposited in BD represents a relatively insoluble byproduct of glycogen metabolism possibly brought upon by an acquired relative deficiency of an enzyme (or enzymes) of the glycogenesis-glycogenolysis pathway.

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Recently Burch[2] provided evidence that people live no longer any more and emphasized that far more research should be undertaken into the factors which regulate aging. His Annotation makes somber reading. He showed that in the U.S.A. expectation of life *at birth* increased enormously in the present century until about 1950 when it reached a plateau. He thought that the expectation may actually be declining.

Although in comparison with the past, a far larger proportion of people nowadays live to a good age, it is not generally appreciated that expectation of life at *late middle age* has remained almost stationary since as far back as records are available. Perhaps the earliest of life tables was constructed in 1687 by Halley[3] of Halley's comet fame. He reported that in Breslau, Germany, expectation of life at 60 and at 80 years averaged about 12 and 5 years respectively. Three centuries later some corresponding data are as follows: Australians in 1955, 17 and 6 years; South African whites in 1960, 17 and 6 years;[4] American Jews in 1965, 15 and 5 years.[3] From this and other information it would seem that while expectation of life *at birth* in the U.S.A. reached its apparent maximum 20 years ago, expectation at *late middle age* in Caucasian populations over a very long period has slightly improved at age 60 years and virtually not at all at age 80 years. For the Jewish population of U.S.A. since 1940 there has been an undoubted decline.

From the graph given by Burch, in the U.S.A. expectation of life at birth has remained steady since 1950 not only for whites but also for non-whites; the mean figure for the former is about 71 years and for the latter about 64 years, a difference of 7 years. This is very surprising. Most if not all would have predicted with assurance that the difference would become progressively narrower with rise in the socioeconomic conditions of non-whites. But this has not been the case. Burch[2] considered the possibility that non-Caucasian races may be genetically programmed to have a shorter life span than whites. He regarded this as unlikely. Yet the possibility cannot be excluded. The most striking situation that comes to mind in this regard concerns Indians in India compared with Indians whose forebears emigrated to South Africa. In 1951 at Ramanagaram in Mysore, South India, a general health study was made on a population of 73 000 rural Indians. It was found *inter alia* that of the leading causes of death the first ten were infections. Of persons 50 year or more 14.5 per cent reached 70 years or more. In South Africa the age structure of three random groups of urban Indians (330 families) living near Johannesburg has been studied. Almost all were in fairly comfortable circumstances. Leading causes of death among them were coronary heart disease, pneumonias, strokes, cancer and diabetes. Of persons aged 50 or more years only 9 per cent had reached 70 or more years. Although the number of families studied is relatively small, the results obtained are in agreement with the Census figures for 1960, namely 11 per cent for the half million Indian community in South Africa.[5] But this figure has decreased since 1951 when it was 15 per cent.[5] In this respect populations normally show an increase not a decrease with time. Thus despite outwardly vastly improved environmental conditions South African urban Indians at *late middle age* have a somewhat lower expectation of life compared with their outwardly far less fortunate compatriots in rural India. In consonance with this information it is interesting to note that among urban dwellers both in India and in South Africa severe atheroma and peak frequency of myocardial infarction apparently occur a decade earlier in Indians than in whites;[10,11] moreover in India there is evidence that urban dwellers in poor circumstances have a greater frequency of coronary heart disease than would be expected.[12] Nor is the situation described peculiar to South African Indians. In an investigation of 140 Malay families in a township in Johannesburg it was found that 85 per cent owned cars and 90 per cent had Bantu servants, yet of persons 50 years or older only 9 per cent were 70 or more years of age. In comparison with the foregoing, the corresponding proportion for South African whites in the 1960 Census was 22 per cent.[5] In England and Wales in 1961 the proportion was 24 per cent.[13] A further fact of importance is that among South African Bantu at a socioeconomic level far below that of local Indians and Malays the corresponding figure was relatively high, namely 17 to 18 per cent.[5] It therefore appears that Indians have a malignant hyperreactivity, possibly of genetic origin, to certain noxious factors which are linked with urban life.[14,15]

Briefly it would seem that:

1. In contexts of modern life, ethnic groups may differ markedly in their apparent maximum expectation of life *at birth*, a stage which appears to have been reached in the U.S.A. by both white and non-whites.
2. In developing populations and in many western populations life expectation at birth is still increasing, the rate of increase is regulated largely but not wholly by the fall in mortality rate of the young.
3. At *late middle age* there have been disappointingly small gains in life expectation over a period of three centuries, if not longer. In some populations—e.g. Jews in the U.S.A.[4] and Indians in South Africa[5]—life expectation at late middle age has declined.

All this is little realized and, as Burch[2] emphasized, is happening in spite of the billions spent on medical services and research.

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Cardiac causalgia and hoarseness

The syndrome of cardiac causalgia major and minor has been described[1,2] The relationship of its manifestations to ischemic heart disease especially to myocardial infarction is well known The development of hoarseness however is not recognized as one of the rare manifestations of this syndrome Hoarseness as a symptom of cardiac causalgia is briefly illustrated by two recently observed patients

N S H a 60 year old Caucasian woman developed an apical infarct in 1956 Since then she has experienced tightness in the chest on exertion The tightness is associated with premature contractions palpitation dyspnea and sweating but no cough Recently the anginal episodes occurred more readily and more frequently The pain developed after very little walking emotional disturbance and excitement and disappeared with rest and sublingual use of nitroglycerin The patient soon began to develop hoarseness and consulted two otolaryngologist neither of whom found any vocal cord paralysis or any cause for the hoarseness With strict and meticulous therapy the angina pectoris has subsided and so has the hoarseness

S L G a 70-year old Caucasian woman developed an anteroseptal infarct in 1965 Her recovery was uneventful except for a lupus erythematous syndrome with L E phenomena produced by quinidine and again by procainamide employed to control frequent premature contractions Except for mild angina pectoris her cardiac state was satisfactory During February 1970 she began to develop frequent episodes of angina pectoris with the slightest exertion Anginal episodes were initiated by mild physical and psychic stress One day in February she developed severe chest pain with dyspnea coughing palpitation and apprehension Several days later she became hoarse as with a laryngitis She was confined to bed for a couple of weeks After her angina pectoris and acute coronary insufficiency had subsided she consulted otolaryngologists who found her larynx and vocal cord to be normal Nevertheless the hoarseness continued With meticulous attention to therapy for ischemic heart disease the angina pectoris lessened by May 1970 and so did the hoarseness With the disappearance of the anginal pain in June 1970 the hoarseness also disappeared An otolaryngologist examined her on several occasions during that period and found no abnormalities

In both patients nitroglycerin had been used on frequent occasion for the anginal pain and had relieved the angina but had no influence on the hoarseness Steroids were not tried in either patient

The mechanism for this syndrome remains unknown as does the mechanism for cardiac causalgia i e a functional disturbance Both patients were treated for ischemic heart disease and advised that there was no organic laryngeal disease As with classical cardiac causalgia their hoarseness gradually disappeared as they adhered closely to cardiac therapy

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Decline and fall?

In the past three of the horsemen of the Apocalypse —War Famine and Pestilence —saw to it that few reached adulthood and that fewer still attained old age Of those who did not die young it was believed that The days of our years are threescore years and ten and if by reason of strength they be four score years yet is their strength labour and sorrow[1] What are the days of our years at present?

Recently, Burch[2] provided evidence that "people live no longer any more" and emphasized that far more research should be undertaken into the factors which regulate aging. His Annotation makes somber reading. He showed that in the U.S.A. expectation of life *at birth* increased enormously in the present century until about 1950, when it reached a plateau. He thought that the expectation may actually be declining.

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3. At *late middle age* there have been disappointingly small gains in life expectation over a period of three centuries if not longer. In some populations—e.g., Jews in the U.S.A.[6] and Indians in South Africa[5,9]—life expectation at late middle age has declined.

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Two hundredth anniversary of self-prediction of sudden, exertional cardiac death

William Heberden gave the first clinical description of angina pectoris to the College of Physicians on July 21 1768 but Some Account of a Disorder of the Breast was not published in the Medical Transactions of the College[1] until February 1772 Later in Chapter 70 on Pectoris Dolor of a book written in Latin in 1782 and published posthumously in 1802[2] after it was translated into English by his son Heberden remarked that of an experience of nearly a hundred cases he had observed only one autopsy examination that of his 5? year old over weight anonymous physician A London physician Dr Unknown on reading Heberden s account was so impressed with the clarity of its presentation that he wrote a letter to Heberden in March 1772 Heberden s account of angina pectoris so exactly correspond (sic) with what I have experienced of late years that it determined me to give you such particulars as I can recollect at these times to have felt more especially as some sensations have frequently led me to think that I should meet with a sudden death Dr Unknown described the phenomenon of enduring the pain (and continued my pace without indulging it) which Osler recognized in 1897[3] and MacAlpin and Kattus[4] in 1966 described as walk through angina Of other sensations which to me seem to indicate a sudden death he was uncertain whether they should be attributed to angina pectoris He had often felt under various circumstances an universal pause within me of the operations of nature for perhaps three or four seconds and when she has resumed her functions I felt a shock at the heart Since Heberden had mentioned in his initial report that several of his patients had died suddenly and were buried before he could examine them Dr Unknown left specific instructions that if he died suddenly Heberden should perform a postmortem examination

In less than three weeks Heberden was informed of the sudden death in less than half an hour of Dr Unknown who was in the midst of a walk which he was taking after dinner Heberden obtained the services of Mr John Hunter and the autopsy was done within 48 hours The patient exhibited great robustness The contents of the thorax were examined with peculiar attention particularly the heart with its vessel and valves and all were found to be in a natural condition except some few specks of a beginning ossification upon the aorta The left ventricle of the heart was remarkably strong and thick It was remarkable that the blood was no where coagulated perfectly fluid being of the consistence of thin cream

Heberden observed that other fellow sufferers noted the sensation of an apparent suspension of life for a few seconds while walking prior to death As noted by Segall in 1944[5] Dr Unknown described the cardiac arrhythmia as ventricular diastole of unusually long duration followed by a very strong heart beat. The patient correctly surmised that his syndrome was dangerous even though he never experienced cardiac pain at rest That his sudden death was probably due to ventricular fibrillation is suggested by the fact that the postmortem examination failed to reveal any disease of the heart and its vessels and valves

This year is the 200th anniversary of self prediction of sudden exertional cardiac death Although sudden cardiac death is still very common the effectiveness of *prompt* defibrillatory treatment has been documented in 7 out of 7 cases of exertional cardiac arrest in patients with coronary heart disease The lack of evidence of evolving myocardial infarction in at least 6 instances[6] and the fact that the first of these patients now 64 years of age has continued physical training gainful employment and outdoor recreation activities without further recurrences of either myocardial infarction or car

diac arre t for over 3 years testifies to Dr Claude Beck s[1] comment about hearts too good to die

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plantation but he made the initial world shattering successes possible He was a quiet publicity shy but active clinical part ner in a big world famous unit

Recognition of his services was soon forthcoming In 1959 he was appointed Director of the Council for Scientific and Industrial Research Cardiovascular Pul monary Research Group at the University of Cape Town and in 1964 was appointed to a personal Associate Professorship of Medicine In 1966 he was R T Hall guest lecturer in Australia and in 1967 was the Honored guest of the American College of Cardiology in Washington D C

Val Schrire was a fine clinical cardiolo gist He trained himself to be precise and recorded and documented every clinical detail in the patients whom he saw This started as a student and he kept carefully the clinical records and photographs of x rays and ECGs of the patients he clerked as a student or treated as an intern and resident He bound his early records in a series of books but an uncontrollable washing machine flooded his basement and damaged many of the later records He built an outstanding personal collection of clinical information in the cardiac clinic He took the histories himself he evaluated them meticulously elicited the physical signs carefully and then dissected the ECG and x ray in detail He dovetailed the clinical data always recording his com ments and analyzing in detail any minor variation from an established clinical pat tern He was a clinical cardiologist and looked to the catheterization laboratory only for confirmation of his clinical assess ment

He worked hard and ran a fine unit He did his work at a trot He followed a simple dictum he worked quickly and if his junior were unable to keep pace they fell by the wayside The good workers re mained the indifferent postgraduates dis appeared

He had a passion for justice and priori ties. He was intolerant of fools sharp medi cal practice or indifferent patient care His colleagues found that he offered the best clinical opinion and service to his patients but he was prepared to correct their errors

He worked hard often 10 to 14 hours a day He could see 40 to 50 patients a day in the outpatient clinic running swiftly from cubicle to cubicle His working speed was unbelievable and occasional visitors were left breathless by his industry

He made daily rounds and never failed to see a patient For many years he also reported on all the hospital ECGs often at the end of a busy day He had a photo graphic memory and could recall fine de tails long forgotten about patients who had been seen years before

He was a delightful teacher and at his best in small groups He spoke well his argument and discussion were pertinent he had an intimate knowledge of the pub lished literature and he had a vast store house of information about unusual indi vidual patients and he could trace their clinical records in minutes

He was a human doctor he seemed to have a cold exterior but he was warm and human to his patients and he could always remember their family details He rarely forgot an item of clinical history and the patients would come back again and again often having to wait for hours in a cold drafty corridor on a hard bench

He made a big impact on cardiology although he made no major break throughs He wrote classical descriptions of Beri beri and The natural history of pericarditis His early research was con cerned with pulmonary stenosis the assess ment of its severity and the detection of an associated ventricular septal defect With Vogelpoel he studied the problem in detail and published the first important studies on the influence of vasoactive drugs on cardiac murmurs He reviewed the clini cal features of the common congenital and acquired disorders of the heart and studied the racial incidence of cardiac disease in the four different racial groups who live in the Western Cape He was interested in the modification of the natural history of car diac disease by an operation and made important long term studies in large groups of patients after correction of Fallot s tet ralogy or after a valve replacement

He wrote two important monographs Clinical Cardiology has reached its third edition in seven years and with Professor C N Barnard he wrote The Surgery of

Obituary

Velva Schrire, M D., F.R.C.P , F.A.C C.

1917-1972



Dr Velva Schrire 1917 1972

Val Schrire has passed and has left a hiatus in cardiology in South Africa He was a brilliant scholar matriculating in 1933 as the top student in South Africa He graduated M Sc in 1938 Ph D in 1940 and M B Ch B (Honours) in 1941 He entered the armed forces and served from 1943 to 1945 He returned to Groote Schuur Hospital to complete a postgraduate medical residency and in 1949 was appointed senior registrar to Paul Wood at the National Heart Hospital This was followed by a short spell under Dr Samuel Levine at the Peter Bent Brigham Hospital

In 1951 he returned to Groote Schuur Hospital, Cape Town, and founded the cardiac clinic For many years the clinic occupied a single room and this he shared with a secretary a technician a nurse, and the patients The room served as a clinic during the day, an electrocardiographic reporting room in the late afternoons, and as a repository for records Gradually, he was allocated more space, a room at a time and often corridors were enclosed to provide space for filing He even shared his catheterization laboratory with the radiology department and only had its use for half of each day

The clinic grew under his guidance and acquired an international reputation It is now the finest clinical unit in the Southern Hemisphere and has few rivals It has trained many clinical cardiologists, it has provided an unrivaled service to the entire country and patients come from all the major centers in South Africa

Dr Schrire was responsible for the development of a flourishing unit for cardiac surgery The diagnosis in patients submitted to surgery was invariably complete and the surgical staff had only to close a defect or correct a valvular deformity He nutured, trained cajoled, guided, and where necessary corrected his surgical colleagues He personally was opposed to heart trans

Letters to the Editor

The reliability of the Holter Avionics system in reproducing the ST T segment

To the Editor

The Holter Avionics system is used for long term recording of the electrocardiogram (ECG) under dynamic conditions The system consists of three main parts (1) a portable tape recorder which records the ECG of the examinee (Electrocardiocorder) (2) an oscilloscope on which the ECG signals recorded by the tape are displayed by rapid super position (Electrocardioscanner) and (3) a unit for printout of the ECG complexes from the tape onto conventional ECG paper (Electrocardiocharter) This system is widely used for detecting transient disturbances in heart rate and rhythm.[1-4] Reports on its use for detection of changes in the ST T segment are scanty probably because of the claim of Hinkle and co-workers[5] that this system introduces artifacts in the ST T segment.

In a previous investigation[6] using the Holter Avionics system we examined the ECG of 39 normal individuals around the clock and did not detect any deviations or artifacts induced by the recording system. Therefore we decided to test the reliability of the system by the following method The ECG of 3 individuals with normal ECG and 3 patients with ischemic ST T changes was recorded through the usual precordial lead of the Holter Avionics system simultaneously by both the magnetic tape of the Electrocardiocorder (Model F) and by the conventional Burdick ECG machine incorporated in the Electrocardiocharter Thereafter the recording from the magnetic tape was transferred onto the Electrocardiocharter and the ECG complexes were again printed out on the Burdick machine Comparing the ECG complexes recorded by the two methods showed a complete similarity except for a slight decrease in the height of the R wave on the tracing obtained through the Electrocardiocorder possibly due to the diminished high frequency of this machine. The similarity of the tracings is demonstrated in Figs 1 and 2

We conclude therefore that the Holter Avionics system can be accepted as reliable for recording accurately the ST T segment and can be used for evaluation of dynamic changes induced by ischemia

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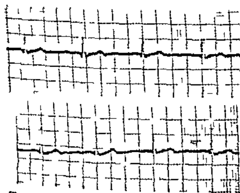


Fig 1 Normal individual *Upper panel* ECG recorded directly on the Burdick ECG machine. *Lower panel* ECG recorded on the magnetic tape of the Electrocardiocorder and subsequently printed out on the Burdick ECG machine.

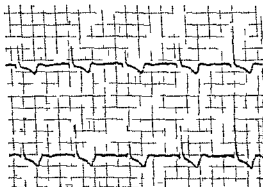


Fig 2 Patient with ST T changes *Upper panel* ECG recorded directly on the Burdick ECG machine *Lower panel* ECG recorded on the magnetic tape of the Electrocardiocorder and subsequently printed out on the Burdick ECG machine

the Common Congenital Cardiac Malformations,' which has been translated into four languages

His greatest contribution was in teaching and in the dissemination of personal knowledge to his students registrars, and colleagues Unlike many of his contemporaries, he did not like being a visiting professor and preferred to remain at home, at work providing a service to his patients and colleagues

Although he worked hard he relaxed at home on Sundays in the garden with his family He was a good father and husband and his family have been deprived prematurely of a good and loving companion

It is tragic that his last year was filled with suffering and pain He remained cheerful and continued to work to the end tidying the clinic, disposing of patients, and completing his unpublished work

He died as he lived a quiet and humble but a very great man

Mervyn S Gotsman, M D

SIGNIFICANT IMPORTANT PUBLICATIONS

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2 Schrire V Experience with pericarditis at Groote Schuur Hospital Cape Town S Afr Med J 33 810 1959
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Letters to the Editor

The reliability of the Holter Avionics system in reproducing the ST T segment

To the Editor

The Holter Avionics system is used for long term recording of the electrocardiogram (ECG) under dynamic conditions The system consists of three main parts (1) a portable tape recorder which records the ECG of the examinee (Electrocardiocorder) (2) an oscilloscope on which the ECG signals recorded by the tape are displayed by rapid superposition (Electrocardioscanner) and (3) a unit for printout of the ECG complexes from the tape onto conventional ECG paper (Electrocardiocharter) This system is widely used for detecting transient disturbances in heart rate and rhythm[1-3] Reports on its use for detection of changes in the ST T segment are scanty probably because of the claim of Hinkle and co-workers[4] that this system introduces artifacts in the ST T segment.

In a previous investigation[5] using the Holter Avionics system we examined the ECG of 39 normal individuals around the clock and did not detect any deviations or artifacts induced by the recording system. Therefore we decided to test the reliability of the system by the following method The ECG of 3 individuals with normal ECG and 3 patients with ischemic ST T changes was recorded through the usual precordial lead of the Holter Avionics system simultaneously by both the magnetic tape of the Electrocardiocorder (Model E) and by the conventional Burdick ECG machine incorporated in the Electrocardiocharter Thereafter the recording from the magnetic tape was transferred onto the Electrocardiocharter and the ECG complexes were again printed out on the Burdick machine Comparing the ECG complexes recorded by the two methods showed a complete similarity except for a slight decrease in the height of the R wave on the tracing obtained through the Electrocardiocorder possibly due to the diminished high frequency of this machine The similarity of the tracings is demonstrated in Figs 1 and 2

We conclude therefore that the Holter Avionics system can be accepted as reliable for recording accurately the ST T segment and can be used for evaluation of dynamic changes induced by ischemia.

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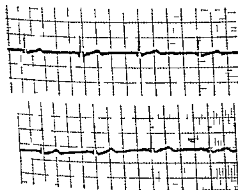


Fig 1 Normal individual *Upper panel* ECG recorded directly on the Burdick ECG machine *Lower panel* ECG recorded on the magnetic tape of the Electrocardiocorder and subsequently printed out on the Burdick ECG machine

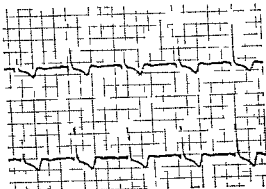


Fig 2 Patient with ST T changes *Upper panel* ECG recorded directly on the Burdick ECG machine *Lower panel* ECG recorded on the magnetic tape of the Electrocardiocorder and subsequently printed out on the Burdick ECG machine.

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Hypertrophic obstructive cardiomyopathy

To the Editor

Hypertrophic obstructive cardiomyopathy (HOCM) is a disease which has attracted wide spread interest but whose natural history remains poorly understood[1-4] Recently it has become apparent that the diagnosis may be made in elderly patients in whom it was clinically unsuspected[5] We report here a lady with long standing cardiac symptoms in whom the diagnosis of HOCM was not made until her eventy seventh year

F C is now a 79 year old Caucasian woman who was admitted to the hospital in July 1970 because of retrosternal pressure sensations and syncopal attacks At age 4 her parents were told that she had rheumatic fever and her activities were restricted throughout childhood and young adulthood She was first told she had a heart murmur when she was 35 years old She retired from school teaching when she was 5? because of progressive exertional dyspnea and fatigue During the next 21 years she became short of breath performing routine household chores had frequent episodes of paroxysmal nocturnal dyspnea and developed retrosternal pressure sensations consistent with angina pectoris and transient bouts of lightheadedness associated with exertion She was treated with digitalis salt restriction and diuretics without apparent success In the week prior to admission her retrosternal pressure sensations became more frequent more prolonged and refractory to nitroglycerine She also experienced syncopal episodes while straining at the toilet

On examination she was a thin elderly lady with a blood pressure of 130/80 and heart rate of 75 per minute The carotid pulse upstroke was bifid and hyperdynamic The second heart sound was normal and an atrial gallop was heard The heart was enlarged and there was a Grade III/VI systolic murmur heard all over the precordium and radiating into both the carotid and axilla A few inspiratory râles were heard at both base There was no hepatosplenomegaly or peripheral edema

The electrocardiogram (ECG) showed first degree heart block and left ventricular hypertrophy The chest x ray revealed cardiomegaly and calcification of the aortic arch Routine laboratory studies were normal The levels of epinephrine and norepinephrine in the urine were respectively 96 3 and 60 1 ng per minute approximately three times normal for our laboratory

An echocardiogram showed definite anterior movement of the anterior mitral leaflet during systole[6] An apex phonocardiogram demonstrated the presence of a fourth heart sound and an early systolic murmur Right and transseptal left heart catheterization were performed Both cardiac output and stroke volume were subnormal A peak systolic pressure gradient was recorded between the left ventricle and the brachial artery at 95 mm Hg and the systemic arterial pulse showed bisferiens pattern with a classical double hump between the peak and the dicrotic notch Left ventricular angiography showed massive symmetrical thickening of the wall of the left ventricle and a normal aortic valve Based on the above findings a diagnosis of HOCM was made

While in the hospital digitalis was stopped and the patient begun on propranolol 40 mg per day In the year and a half since discharge the patient has done well on propranolol and furosemide 40 mg every other day She no longer has syncope or retrosternal pressure sensations Although her exercise tolerance has not improved she has noted an increased sense of well being At the time of this writing (April 1972) she is feeling fine

The medical histories of 29 family members in five generations were obtained We examined six relatives because of symptoms suggesting heart disease none of whom had evidence of HOCM by physical examination chest fluoroscopy or ECG

This lady s case history is enlightening in that it illustrates how HOCM may be present in the elderly who have been considered to have other forms of heart disease for many years She is unique because she is the oldest patient yet reported with this condition and because of the long relatively benign course of her illness

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Trends in training physicians

To the Editor

I note with interest and disagreement that the educators of America consider a general but adequate knowledge of medicine impossible—in short there is too much to learn.[1] In view of the extensive mass of ever increasing knowledge the brains of even the superior and highly selected youths of America are unable to cope with it all The solution offered by the educators to the problem of the ever increasing knowledge is to reduce the length of time devoted to learning medicine They give up! The objective is to reduce the training period to three years Some shout with pride that they train doctors in 2 years or even one and one half years. In fact some do not even have to learn much at all to become physician assistants.

The emphasis is on the quantity of doctors produced. The advocators of this plan fail to realize that such a practice will only produce an extra year or two of graduates and then the shortened learning period will not even produce greater numbers only less qualified physicians

Our Russian counterparts realize there is more to learn and that a longer period is required to learn it They therefore have increased their training period from 5 to 7 years They emphasize quality scholarly pursuit and research.[2] We reduce our learning time from 4 to 2 years or even 1½ years and emphasize quantity.

Sir should this attitude and practice continue the center of world medicine will move from America to Russia within the next 10 to 20 years! Patients of all countries will look to Russia for special care and the youths of the world will seek Russian diplomas, certificates of special training and advanced education

Why not emphasize quality scholarly pursuit and research as well as quantity? Why not 300 more medical schools with classes of only 75 students or less with adequate scholars of medicine as teachers? Why did some medical school and educators express pride in their small classes (75 or fewer students) less than 10 years ago but now large classes are the thing of the time? Sir money is the answer! Yes but what about sick people and lives With all the great advancements of modern times people still long to live longer but live no longer any more

If you could only help to awaken the educator

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Atrioventricular interaction in isorhythmic dissociation

To the Editor

In November 1971 and in January 1972 Levy Damato and Bobb and Lulay and Damato published two papers referring to the mechanism of synchronization in dogs and in men respectively in this JOURNAL From our own studies on the subject carried out on cats[1] and from previous observations in patients with artificial cardiac pacemakers[2] we can confirm the findings of these authors in most points of view There are some striking differences however with respect to the effect of atrial stretching Since Damato and co-workers do not know our papers from 1965 and 1969 we should be glad to give some comments to the problem mentioned above

The experiments were carried out in 52 anesthetized cats which remained in spontaneous rest rhythm Right ventricular pacing was performed by a transvenous approach Aortic pressure right atrial pressure and right atrial ECG were studied in every case Like Damato and co-workers and in contrast to Levy and Zieske we preferred to study the mechanism of synchronization in animals with intact A-V conduction systems Five cats were studied which previously had been treated with reserpine vagotomy was performed in 26 cats and beta adrenolysis with propranolol was done in 20 animals In five cats experiments were carried out with constant aortic pressure and in eight others with constant right atrial pressure

Our results were similar to those of Damato and co-workers and of Levy and Zieske with respect to the changes in aortic and right atrial pressure and with respect to the frequency in the appearance of synchronization phenomena In contrast to Levy and Zieske however synchronization did not cease when the aortic pressure was kept at a constant level

To illustrate we may be allowed to represent a segment of an original experiment in which the decrease of aortic pressure during asynchronous ventricular pacing was prevented by unclamping a tube leading from the central aorta to a reservoir elevated to a height equivalent to the prevailing mean aortic pressure (Fig 1) At arrow 1 ventricular pacing begins with a rate little above the spontaneous sinus rate At arrow 2 the ventricles become depolarized by the artificial pacemaker whereas the atria are excited on a retrograde pathway An increase of right atrial pressure can be observed whereas the aortic pressure remains constant At arrow 3 the rate

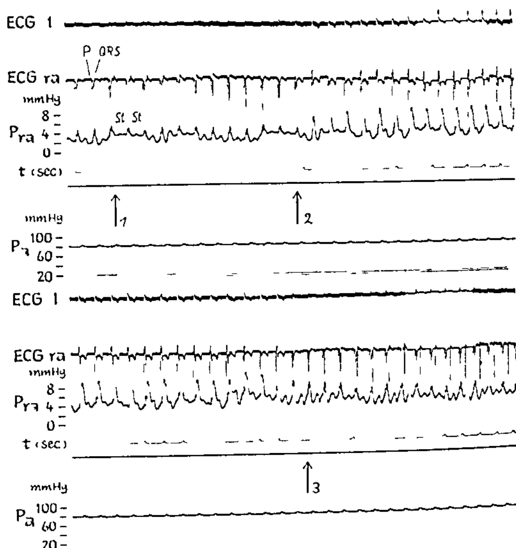


Fig 1 Section from synchronization experiment No 164 (aortic pressure at a constant level) Spontaneous sinus rate 67 per minute pacing frequency 69 per minute *ECG 1* = ECG Lead I *ECG ra* = right atrial ECG P_r = right atrial pressure P = aortic pressure Time marker (t) denotes seconds The records of the top half of this figure are continued in the bottom portion

of sinus node has exceeded the fixed pacemaker rate the temporal relationship between atrial and ventricular contraction has normalized and the atrial pressure decreases Under these hemodynamic conditions the frequency of the sinus node begins to decelerate toward its initial value If the pacemaker rate always is drawn near the accelerated sinus rate synchronization can develop as described by Levy and Zieske[4] and by Paulay Damato and Bobb[5]

Fig 2 demonstrates a diagrammatic representation of the whole experiment a segment of which was shown in Fig 1 Depolarization of the ventricles prior to the atria (hatched field) leads to sinus rate increase After this period sinus rate begins to decrease

There is another argument which confirms our assumption that arterial blood pressure fluctuations cannot be the crucial mechanism of synchronization. Frequent atrial pacing leads to decrease in aortic pressure too (by insufficient diastolic filling of the ventricles) but sinus rate does not increase On the contrary there is to be observed a decrease in sinus rate

In agreement with Paulay Damato and Bobb[5] we suggest that stretching of the sinus node fibers plays the most important role in accelerating sinus rate Effective stretch however cannot be produced by extension of the entire atrial wall as elucidated from our experiments with constant right atrial pressure (see Fig 13 and Table VIII in our article from 1969[3]) The crucial mechanism of sinus rate acceleration which may lead to synchronization of atria and ventricles in animals and in men is in our opinion stretching of sinus node fibers by atrial contraction against the closed tricuspid valve

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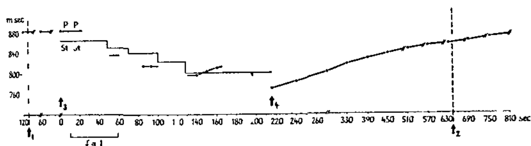


Fig 2 Diagrammatic repre entation of synchronization experiment No 164 At arrow 1 the aortic pressure fluctuations were attenuated by unclamping a tube connecting the central aorta with an elevated reservoir At arrow 2 the clamp was reapplied Arrow 3 demonstrates the beginning and arrow 4 the end of artificial pacin

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Reply

To the Editor

We read with interest the data summarized in the letter above by Drs Diederich and Djonlagic Our observations in dogs in which right atrial pressure was controlled by an atrial vent show the contribution of right atrial pressure changes to the mechari m of synchronization of atria and ventricles in isorhythmic dissociation (unpublished findings) The results of acute extrinsic cardiac denervation experiments (Reference 5 above) indicate that arterial baroreceptor reflexes are involved also Thus we consider that ***both*** arterial and right atrial pressure change are important factors in the mecha ni m of A V synchronization in man.

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Book reviews

STROKE REHABILITATION—*A Guide to the Rehabilitation of an Adult Patient Following a Stroke*. By Harry T. Zankel, M.D. Springfield, Ill., 1971, Charles C Thomas, Publisher. 284 *pp*. *Price $15.75*.

Stroke *rehabilitation* is an extremely important subject in medicine at the *present time*. Zankel presents rehabilitation primarily from the physical point of view. The book *contains* many good photographs of patients *receiving* various forms of physiotherapy. The text is rather loosely written, however, and lacks adequately detailed information. For example, on page 138 no specific data are presented as to the type of drug, dosage, etc., that should be *used for thalamic* pain. The management of the shoulder-hand syndrome is also lacking in specific details which are needed by the *practicing* physician. Although rehabilitation of the patient with a stroke is important, this *book is not* very helpful because it deals with generalities.

ECG DIAGNOSIS SELF-ASSESSMENT. By Edward K. Chung, M.D., F.A.C.P., F.A.C.C., and Donald K. *Chung, M.D.* *Hagerstown*, 1972, Medical Department, Harper & Row, Publishers, Inc. *221 pages*. *Price $17.95*.

In this atlas, clear *illustrations* of a wide variety of *electrocardiograms* are presented in a fashion to test the reader's ability to interpret ECGs. The authors *present* each tracing with a very brief *clinical summary* along with the ECG on one page and the interpretation on the *reverse side*. This *manner* of presentation allows the student to make his interpretations and then check them with the authors. The 200 ECGs are *fairly common ones*. However, some are seldom encountered even in a busy internist's practice. A reader who can interpret these tracings properly would have a good knowledge of electrocardiography. This is a very good *manual*.

CIRCULATORY EFFECTS AND CLINICAL USES OF BETA-ADRENERGIC BLOCKING DRUGS. Edited by Donald C. Harrison, M.D. Amsterdam, 1971, Excerpta Medica. 147 pp. Price $12.50.

The use of beta adrenergic blocking drugs is increasing constantly. It is *therefore necessary* that the physician be thoroughly acquainted with the mechanism of action of these drugs as well as their indications and value in various cardiac disease states. Harrison and his associates review the action of these drugs and their uses in *9 brief* chapters. They discuss in about 140 pages the pharmacology, circulatory effects, and use of *these drugs* in angina pectoris, in arrhythmias, myocardial infarctions, *hypertrophic* subaortic stenosis, *hypertension*, hyperthyroidism, and other diseases. The contraindications and limitations are also presented. Unfortunately, their discussions of the use of these drugs in the various *clinical states* emphasize the drugs themselves but *fail* to indicate strongly the importance of integrating the administration of the drugs along *with other* important therapeutic measures such as *diet*, *smoking*, caffeine intake, digitalis, antiarrhythmic agents, and rest. The experienced *clinician* will find this short book more helpful than the beginner. The latter, of course, will learn much about these drugs in Harrison's book *but he* must realize they represent only one cardiac agent. The publication is a good one.

THE SINOATRIAL PACEMAKER OF THE HEART. By Chandler McC. Brooks and Hsin-Hsiung Lu. Springfield, Ill., 1972, Charles C Thomas, Publisher. 179 *pp*. *Price $15.50*.

This important short monograph should interest all students of medicine and physiology, but especially cardiologists and other physicians who have a special interest in cardiology. Brooks and his associates have had an interest in pacemakers of the heart for many years. The sinoatrial node is of special importance. The authors in less than *150* pages review the anatomy of the S-A node, development of the impulse, the electrophysiologic properties of the node and its response to various *factors* including pathologic states and arrhythmias. A good bibliography is included. Some of the historical comments are interesting, especially the role of Keith and Flack *in the discovery of* the S-A node. The illustrations are good and the discussion of action potential traces as influenced by various factors such as electrolyte concentrations are all recent important contributions. This is a very good and important book. It is especially timely in view of the *relatively intense interest in* electrophysiologic phenomena of the heart and the diagnosis and management *of cardiac arrhythmias*.

ACUTE CORONARY CARE. By Gerald H. Whipple, M.D., et al. Boston, 1972, Little, Brown & Company. *383* pp. Price $11.50.

Several books and booklets have appeared recently on the *CCU* and the intensive care of the patient with acute coronary disease. Each one has its own *features*. This one is fairly extensive. It is

of value for nurses other attendants and physicians. The authors emphasize the practical aspects of coronary care and present the various chapters to educate the beginners as well as the more experienced person. There is nothing really new in this monograph but it presents a good course in acute coronary care and progressive coronary care. The concept of the CCU nature of coronary heart diseases anatomy and physiology of the heart and lungs infarction nursing electrocardiography arrhythmia resuscitation and cardioversion are among the many aspects discussed. Dr Whipple s preface is interesting and the selected bibliography illustrations and index are all good. This monograph is worth owning as well as worth studying especially by nurses but also by physicians as well.

Clinical Cardiac Roentgen Diagnosis By Alphons Jacob M D St. Louis 1972 Warren H Green Inc 309 pp Price $19 50

This short discussion of Clinical Cardiac Roentgen Diagnosis should be of interest to interns residents and medical students as well as busy practitioners. The book of about 300 pages contains clear and well selected reproductions of roentgenograms supported by a lucidly written text. The book is liberally illustrated. There is nothing unique about the volume however its small size and brevity along with the many illustrations should interest physicians who wish to review cardiac roentgenography quickly. This is not a reference book but it is a good short treatment of the subject

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Books received

RESEARCH IN DISEASES OF THE TROPICS—British Medical Bulletin Vol 28 No 1 January 1972 C L Gordon Smith Scientific Editor London 1972 The Medical Department The British Council 102 pages Price $6 50

CARE OF THE CRITICALLY ILL CHILD By R S Jones M D and J B Owen Thomas M B Ch B M D Baltimore 1971 The Williams & Wilkins Company 323 pages Price $20 75

CHANGING CONCEPTS IN CARDIOVASCULAR DISEASE Edited by Henry I Russek M D and Burton L Zohman M D Baltimore 1972 The Williams & Wilkins Company 469 pages Price $23 75

PERIPHERAL VASCULAR DISEASES Ed 4 By John L Fairbairn II M D John L Juergens M D and John A Spittell Jr M D Philadelphia London and Toronto 1972 W B Saunders Company 197 pages Price $25 00

PLASMA LIPOPROTEINS Biochemical Society Symposium No 33 held in University College London April 1971 Edited by R M S Smellie London and New York 1971 Academic Press Inc. 165 pages Price $8 95

HEART ATTACK YOU DON'T HAVE TO DIE By Christiaan Barnard New York 1971 Delacorte Press 178 page Price $6 95

PROGRESS IN CARDIOLOGY By Paul N Yu M D and John F Goodwin M D Philadelphia 1972 Lea & Febiger Publishers 283 pages Price $15 00

Announcements

International Symposium on Cardiac Pacing

The IVth International Symposium on Cardiac Pacing will be held in Groningen the Netherlands on April 17 19 1973 in the Congress Centre Martinihal

Organized by the State University of Groningen the Dutch Society of Cardiology and the Dutch Heart Foundation topic will include basic principles of cardiac stimulation world survey of cardiac pacing pacing systems energy sources electrodes stimulation threshold exceptional indications for cardiac pacing interference ECG s in cardiac pacin pacing in myocardial infarction pacemaker clinics and follow up systems Each area will include a general survey and an outline of the latest development

Fees will be 170 Netherland florins (U S $50) for participant and 100 Netherland florins (U S $30) for accompanying guests For further information please write Dr H J Th Thalen Secretary General Secretariat Symposium on Cardiac Pacing Dept of Cardiology University Hospital Groningen the Netherlands

Subspecialty Board on Cardiovascular Disease

Requirements for examination

A. PREREQUISITE

The candidate must be certified as a Diplomate in Internal Medicine or must have passed the Qualifying Written Examinations of 1969 or 1970 before applying for examination The candidate may apply for the examination after completing six months of his second year of training in cardiovascular disease but he must complete his formal full time training in cardiovascular disease before taking his Subspecialty Board Examinations No additional applications are being accepted for the current oral examination

During the period January 1 through March 15 1972 completed applications are being accepted for the new examination in Cardiovascular Disease The written component of the examination will be held October 17 1972 at various centers in conjunction with written examinations in other subspecialty field In addition to this written examination candidates for the Subspecialty Board on Cardiovascular Disease must pass an oral examination to be administered after December 31 1972 The oral examination will be given at smaller regional examinations in addition to larger national examinations

Applicants for the examination to be offered on October 16 1973 should request an application form in January 1973

B TRAINING

Requisite for general internal medicine The candidate must be certified as a Diplomate in Internal Medicine (or have passed the Qualifying Examinations of 1969 or 1970)

In regard to the training in the broad field of internal medicine the *Policies and Procedures* of the American Board of Internal Medicine December 1970 read as follows in their relationship to the requirements for the Certifying Examination in general internal medicine

Important note on minimum aspects of requirements The Board recommend that candidates receive three years of training in the broad field of internal medicine whether they plan to practice internal medicine or a subspecialty It is recognized that some candidates can undertake the examination with a *minimum* of two of the three years of training in general internal medicine These exceptional candidates must obtain authorization from the director of their second year of training in internal medicine The Board will request from the director documentation of such authorization during the process of evaluation of the candidate s application for the examination

Requisite cardiovascular training The current requirements of the American Board of Internal Medicine for subspecialty certification adopted in 1970 are

Two years of full time graduate education in the subspecialty (This education must be completed in a program approved for three years of residency in internal medicine by the Residency Review Committee in Internal Medicine under a physician competent in the subspecialty field A period of education in another institution may be acceptable however the institution must have a recognized reputation for advanced educational programs in the subspecialty and provide this in an academic atmosphere)

Except in the most unusual circumstances the candidate for certification by the Subspecialty Board on Cardiovascular Disease should have devoted the equivalent of one of the two years in training to the broad area of clinical cardiovascular disease including experience in the intensive care of patients with acute cardiovascular disorders

The earlier policy involving *diplomates* initiating residency training in internal medicine before July 1 1970 stipulated four years of training in internal medicine and cardiovascular disease after completion of an internship Although only one year of specific cardiovascular training was required most candidates had completed two years of training in cardiovascular disease It is the policy of the Ameri

can Board of Internal Medicine that if candidates have undertaken less than the required two years of appropriate subspecialty training their acceptability will be decided upon by the Executive Committee after review of their training and other credentials As already indicated these requirements specified in this paragraph apply to candidates initiating residency training in internal medicine before July 1 1970

C EXAMINATION

The subspecialty examinations in Cardiovascular Disease are designed to demonstrate that the candidate possesses certain specialized knowledge and has acquired particular skills that entitle him to be known as a consultant to other internists Candidates will be required to pass both a written and an oral examination The written examination will test the following areas

(1) Normal and pathologic anatomy and physiology of the circulatory system

(2) Interpretation of electrocardiograms cardiovascular roentgenograms and special procedures and techniques used in the study of cardiovascular problems The candidate should be able to integrate the information from these sources in such a way as to lead logically to the proper diagnosis and treatment.

(3) Knowledge of the pharmacology including side effects and therapeutic applications of drugs used in the treatment of cardiovascular diseases

(4) Knowledge of the indications contraindications and complications of other forms of treatment including surgery

(5) Familiarity with the several aspects of cardioversion and cardiac pacing as well as other specialized techniques useful in non operative therapy and/or diagnosis

(6) Interpretation of hemodynamic data obtained from the catheterization laboratory

(7) Familiarity with the medical aspects of ca diovascular surgery

(8) Knowledge of contemporary cardiovascula literature

(9) Competence in the general field of interna medicine

The oral examination will consist of the evalu tion of two patients with cardiovascular problem

(1) The candidate must be proficient in takir an accurate history and in performing a detaile physical examination

(2) The candidate must convincingly demo strate to his Board examiners his ability to integra and synthesize cardiovascular data and to serve a consultant in cardiovascular disease to a wel trained internist

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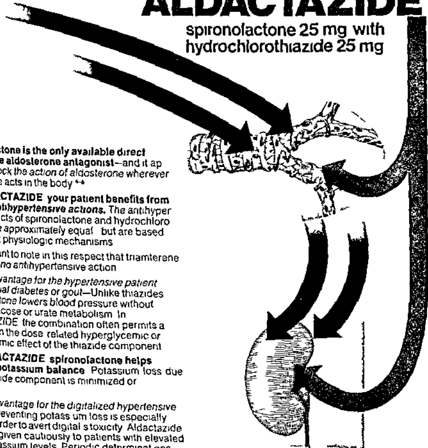
E RE EXAMINATION

(1) The interval between examinations will be not less than one year

(2) A candidate who has failed three written or two oral examinations of the Board of Cardiovascular Disease must present satisfactory evidence of the completion of additional formal training (at least one year of full time training) before readmi sion to examination

F REQUESTS FOR APPLICATION FORMS SHOULD BE ADDRESSED TO Executive Director American Board of Internal Medicine 3930 Chestnut Street Phila delphia Pa 19104

...you'd see the reasons for starting antihypertensive treatment with



Spironolactone is the only available direct competitive aldosterone antagonist—and it appears to block the action of aldosterone wherever aldosterone acts in the body

With ALDACTAZIDE your patient benefits from additive antihypertensive actions. The antihypertensive effects of spironolactone and hydrochlorothiazide are approximately equal but are based on different physiologic mechanisms

It is important to note in this respect that triamterene has little or no antihypertensive action

Special advantage for the hypertensive patient with potential diabetes or gout—Unlike thiazides spironolactone lowers blood pressure without altering glucose or urate metabolism In ALDACTAZIDE the combination often permits a reduction in the dose related hyperglycemic or hyperuricemic effect of the thiazide component

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Special advantage for the digitalized hypertensive patient—Preventing potassium loss is especially critical in order to avert digitalis toxicity Aldactazide should be given cautiously to patients with elevated serum potassium levels Periodic determinations of serum potassium will guard against the possibility of either hyperkalemia or hypokalemia

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Dosage and Adm ni t ation—Fo esse tial hyper te sion the da ly ad It dosage is two to fo r tab... lets n d ded doses cont nue treatment for two weeks or longe Adj st the dosage accord ng to the esponse of the pat ent Red ice the dosage of othe a t hyper n e agents part cularly gangl o c block ng age ts by 50 percent since Aldac... to ide potentiates t e act on of such d gs For **edema, ascites a effusions n adults** the average dosage s one tablet fou t mes da ly dosage may arye f om one to e ght tablets da ly n d ded doses The da ly dosage of Aldactaz de n ch ldren shou d pro ide 0 75 to 1.5 mg of A dactone (p... ...o body we ght

References 1 Hollander W and others C c Res S ppl 1 to vols 18-19 1 35—I 47 (J ne) 1966 2 Mendlow tz M and others Am Heart J 67 397 409 (Ma ch) 1964 3 La ler D P and o hers (Edi tors) Aldoste one MedcomLea g Systems New York N Y Med cal Commun cat ons Inc 1969 p 45 4 Crabbe J Acta Endocr nol (Kbh) 47 419 43 (Nov) 1964 5 L ddle G W Arch Intern Med 102 998-1004 (Dec) 1958 6 Liddle G W Ann N Y Acad Sc 139 466-470 (Nov 22) 1966 7 V olf R L and othe s J.A.M.A 198 1143-1149 (Dec 5) 1966 8 Johnston L C and Gr ble H G Arch Intern Med 119 225-231 (March) 1967 9 N cke son M n Goodman L S and G lman A (Edi tors) The Pharmacolog cal Ba s of Therapeutics ed 4 New York, The Macm llan Company 1970 pp 731 732

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